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FREE OPERANT RATIO AVOIDANCE
BEHAVIOR IN THE RAT: EFFECTS OF
METHYLPHENIDATE

by



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The undersigned certify that they have read,
and recommend to the Faculty of Graduate Studies for
acceptance, a dissertation entitled "Free Operant
Ratio Avoidance Behavior in the Rat: Effects of
Methylphenidate", submitted by James A. Browne in
partial fulfillment of the requirements for the degree
of Master of Science.

ABSTRACT

Rats were initially trained to respond on a fixed ratio (5) free operant avoidance schedule. Manipulation of the response-shock interval resulted in 'high' rate R*S 20 sec. animals and 'low' rate R*S 80 sec. animals. Periods of variable interval 'free' shock, common to both R*S 20 sec. and R*S 80 sec. animals, were found to maintain response rates engendered by the ratio control conditions in the individual animals. The effects of methylphenidate in a range of dosages (4, 8, 12 and 16 mg/kg), over a series of test procedures, are interpreted in terms of the results pertaining to time of injections, fixed ratio and variable interval responding, and the effects of shock frequency. Overall rate increases at all dosages were observed in most subjects as compared with rates engendered by control conditions. The role of shock frequency as a significant determinant of drug-rate interaction effects is discussed.

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INTRODUCTION

BEHAVIORAL PHARMACOLOGY

Behavioral pharmacology today has become a legitimate area of enquiry within psychological science. As early as 1898¹ physiological journals were appearing with animal experiments investigating drug-behavior relationships; although the restrictions imposed by available behavioral techniques severely limited the scope of such investigations.

It is interesting to note that historically, those investigators who have had immense impact upon psychological science, are often the precursors of present behavioral pharmacology. By the early 20th century Pavlov and Lashley were demonstrating the action of stimulant drugs. Lashley (1917) was concerned with the effects of strychnine and caffeine upon rate of learning. Pavlov (1927), on the other hand, utilized caffeine in studies on differentiation (a type of internal inhibition). "Again if the general excitability of the central nervous system has been increased, for example by an injection of caffeine, the previously established differentiation similarly becomes disturbed" (Pavlov, 1927, p. 127). By 1937

¹

Stewart (1898) - decrease in general activity level of laboratory rat following alcohol ingestion.

Skinner (Skinner and Heron, 1937) was investigating the effects of caffeine and benzedrine upon conditioning and extinction.

In a review of behavioral pharmacology Brady (1957) has pointed out that: "... the history of experimental work in this area amply attests to the numerous difficulties involved in the selective definition of specific drug activity at the neural and behavioral levels. The promise of more precise experimental control and operational definition, however, has encouraged a base behavioral pharmacological literature over the past [65 years] or more, although such experimental efforts on animals have seldom been systematic and the results have almost always been controversial". (p. 719).

Among the many advances in psychological science made in the past several years, one group of contributions emerging from animal laboratory approaches to the experimental analysis of behavior seems to stand out with particular prominence in considering methodological advances in behavioral pharmacology. Reference here is made to the development of operant conditioning (Skinner 1938) techniques in the analysis of behavior and the application of such methods to a wide variety of experimental problems in comparative and physiological psychology. Numerous individual experimental reports

in current psychological, physiological and pharmacological journals have begun to indicate the broad range of investigative areas in which such behavioral control techniques have been found useful.

The basis for this enthusiastic acceptance of the free operant in behavioral pharmacology is not difficult to discern when consideration is given to the rather pressing need for sensitive and reliable preclinical assay techniques and the woefully inadequate answer to this problem that is provided by the extensive early literature in the area.

The great increase of interest in behavioral pharmacology during the last few years has not been due to the formulations of new theories or the impact of cogent arguments. It has been due mainly to the remarkable success which experimental pharmacologists and observant clinicians have had in discovering new drugs with hitherto unsuspected kinds of effects on behavior (Dews, 1958 (a)). This success has made it extremely important that a basic science of behavioral pharmacology should develop as fast as possible.

The first difficulty facing experimental behavioral pharmacology is the complexity of behavior. Physiology is complicated too, yet it has found that an understanding of the effects of a drug on the physiology of an animal

can be attained if the effects are studied system by system, even cell by cell. It would seem reasonable to study the effects of drugs on behavior in a similarly analytical way. One method of doing so is to use operant techniques to study the frequency of occurrence of a 'given' response; whose occurrences can be recorded objectively, and which the animal can make repeatedly in a reasonable period of time. The factors which determine the distribution of occurrences of the responses in time can then be studied.

Many drugs have been shown to influence the rates with which animals make responses of this kind. Dews (1958 (a)) has suggested that the effects of a given drug dosage depend on four classes of factors: -

1. Genetic factors: - the species of the animal, and the particular individual chosen.

2. The nature and frequency of the response under experimental conditions.

3. The nature of the environment: - the eliciting, reinforcing and discriminative stimuli.

4. The previous history of the animal in terms of the training procedures employed and administration of drugs leading to possible adaptive or simulative effects.

A representative example of the work being done in this area is an experiment reported by Dews in 1958 (a).

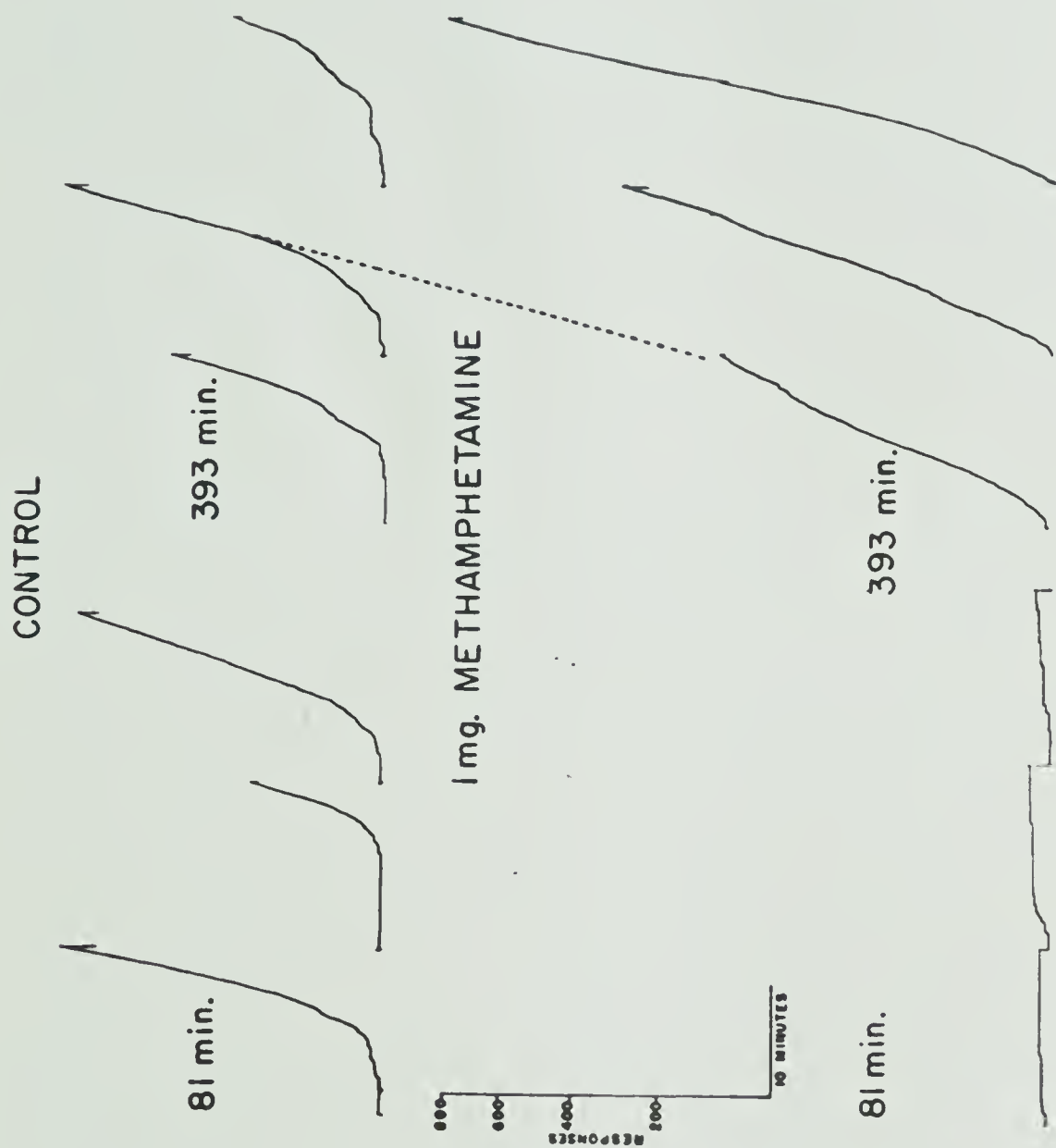
After a food deprived pigeon was trained to peck at an illuminated plastic key, it was given access to the key for a few hours each day. Within several sessions a stable fixed interval, 15 minutes, patterning of behavior emerged. (See Figure 1(a)). Administering methamphetamine to the pigeon on this FI 15 minutes schedule, Dews found that the characteristic effect of the drug is to lead to an increase in the number of responses made per interval (See Figure 1(b)). The maximum rate of responding, however, is not increased, instead, the animal responds steadily at the beginning of the interval at a time when, under control conditions, there is little or no responding.

Since this early work many germane points with respect to the effects of drugs on behavior have become increasingly clear.

The terms "stimulant" and "depressant" as a simple qualifier of "drug", have outlived their usefulness (Dews 1962). One of the best established results in behavioral pharmacology is that the "stimulant" or "depressant" action of drugs does not occur in equal measure on all aspects of behavior. It has been demonstrated repeatedly that a given dose of a drug in a given organism may cause "stimulation" of some behavioral activities and simultaneous "depression" in the sense of increased and decreased

Figure 1

Effects of methamphetamine on fixed interval performance in the pigeon. (Reprinted from Dews, 1958(a)).



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FIG. 1. Effects of methamphetamine on fixed interval performance in the pigeon. *Ordinate*: cumulative number of responses. *Abscissa*: time with key light on. The pen resets to the base line at each reinforcement. The figure shows samples of the performance at two periods during the daily session. Note the initial 'depressive' effect of the large dose of methamphetamine. The dotted line was added to show that the maximum rate following methamphetamine did not exceed the maximum control rate.

output respectively of the behavior according to the method of measurement in use.

An example of this specificity of drug action can be found in the behavioral work on chlorpromazine. Verhave, Owen and Robbins, (1958) utilized a schedule in which the baseline was composed of two components, avoidance behavior and escape behavior. According to Verhave's arrangement, the rat was placed in a box containing a grid floor which could be electrified and a wheel which the animal could turn to avoid or escape the shock. A buzzer was sounded seven seconds before the shock was scheduled. If the rat turned the wheel during the buzzer, the shock was not delivered (avoidance behavior). However, if the animal failed to respond, the shock followed and was terminated only when the animal did turn the wheel (escape behavior). Once the animals were trained to avoid the shock on better than 95 percent of the buzzer trials, the author's administered chlorpromazine in a range of doses. They found that the avoidance was much more sensitive to the drug than was the escape behavior in that a dose of chlorpromazine which caused an avoidance loss of more than 80 percent (ie., the rat responded to the buzzer on less than 30 percent of the trials) caused an escape loss of less than 5 percent.

The repeated administration of some drugs may result

in tolerance effects. Schuster and Zimmerman (1961) found that the increase in response rates generated by .75 to 1.5 mg/kg of dl-amphetamine was considerably smaller after repeated doses. However, they also found that the elevation of locomotor activity, measured separately in the same rats, did not decrease with repeated doses. The authors concluded that with the tolerance effect, an interaction with the schedule parameters (DRL 17.5") is also involved along with physiological determinants.

The terms stimulation and depression are also used by neurophysiologists and neuropharmacologists, usually in the sense of increased and decreased rates of firing of nerve cells. Dews (1962) has stated that: "It is obvious that there is no simple isomorphic relationship between stimulation and depression in the behavioral and in the neurophysiological senses, and in fact, no necessary direct relationship at all". (p. 438).

There is little doubt that the inter-relationship between drug effects and environmental variables is an extremely sensitive one. A primary concern, therefore, in behavioral pharmacology, is how the behavioral effects of drugs are modified by past and present environmental determinants of behavior. Normally an attempt is made to hold these environmental determinants constant, and there-

to minimize their importance in determining the effects of drugs on behavior.

The LD50 of amphetamine and related compounds is greatly dependent on environmental circumstances. This was first reported by Gunn and Gurd (1940), and has subsequently been studied by Chance (1946), and by Höhn and Lasagna (1960). The aggregation of several mice in a cage after the administration of amphetamine reduced the LD50 to of the order of one-tenth of the dose necessary for mice in individual cages. Ambient temperature, size of cage, state of hydration and ambient noise also had effects, although smaller, (Chance, 1946, 1947). It sometimes comes as a surprise, therefore, to find that seemingly trivial factors of the sort that often are not specified in reporting results about the behavior of intact animals can profoundly modify the effects of drugs.

When we deal with less gross dependent variables than life or death, the environmental variables are even more important in jointly determining the net behavioral effect of a drug. Most drugs have selective actions on behavior in different situations so that one cannot predict what the behavioral effect of a drug will be unless something is known about the conditions under which the drug is acting and about the determinants of behavior in that situation.

Morse (1962) has suggested that: "since the selective modification of behavior by drugs is the rule rather than the exception the problem for behavioral pharmacology today is to go beyond the mere demonstration of differences. It must systematize and clarify the nature of the interactions between the effects of drugs and environmental determinants of behavior. A first step is to isolate and specify more exactly which environmental variables are most important in influencing the action of a drug on behavior". (p. 275).

FREE OPERANT AVOIDANCE

Operant psychology is the intensive investigation of the relationship between an organism and its environment. The animal laboratory has provided an opportunity for the systematic analysis of orderly relations among behavioral segments within this framework, and the term "operant behavior" (Skinner, 1938) has been used to refer to behavior which operates upon the environment in this fashion. The process of manipulating such behavior as a function of its environmental consequences has been termed "operant conditioning".

Skinner (1938) first described operant conditioning procedures of the kind that most current behavioral exper-

iments use. Ferster (1953) has pointed out, however, that only experiments with certain additional characteristics are consistently referred to as operant conditioning experiments in current psychological terminology. The present investigation incorporates these additional characteristics:

1. The extensive use of rate and pattern of responding as dependent variables.

2. Schedule-controlled behavior. A schedule of reinforcement is a precise specification of the plan according to which discriminative and reinforcing stimuli will be presented. The use of different schedules of reinforcement gives the investigator extremely powerful control over a variety of rates and patterns of responding.

3. The animal must emit an appropriate response in order to produce the reinforcing stimulus. When such stimuli follow a response they increase the likelihood that the animal will behave in the same way again.

4. The choice of pigeons pecking discs and rats or monkeys pressing levers as the response measure is not entirely arbitrary. When we are dealing with a selected segment of the behavior of a freely moving animal it is essential that the response chosen for study should be one that can be repeated frequently and over long periods without fatigue.

5. The responses studied are usually easy to record by means of automatic equipment.

With these additional characteristics, operant conditioning techniques have been used to investigate a wide range of problems including drug-behavior relationships.

A versatile and efficient way to assess the behavioral effects of drugs in animals is to measure the alterations which the drugs produce on a stable baseline of on-going behavior. This method of measuring the effects of pharmacological and physiological (and many other) variables has been perhaps most forcefully advocated by Sidman (1960). When there is a stable and well controlled "behavioral baseline" only a small number of experimental subjects are required for detecting and measuring relatively minute drug effects. Problems of inter-animal variability are minimized since each animal serves as its own control. Temporal, sequential, and interactional processes can be followed in the individual animal, thus avoiding the blurring of process outlines that result when data must be combined from different animals.

The stability of the baseline within and between experimental sessions makes the avoidance procedure suitable for measuring the effects of repeated admin-

istration of drugs. The free operant avoidance² procedure (Sidman, 1953a) has features that amply justify its extensive use both in routine examination of new drugs and in definitive studies of drug action (Heise and Boff, 1962).

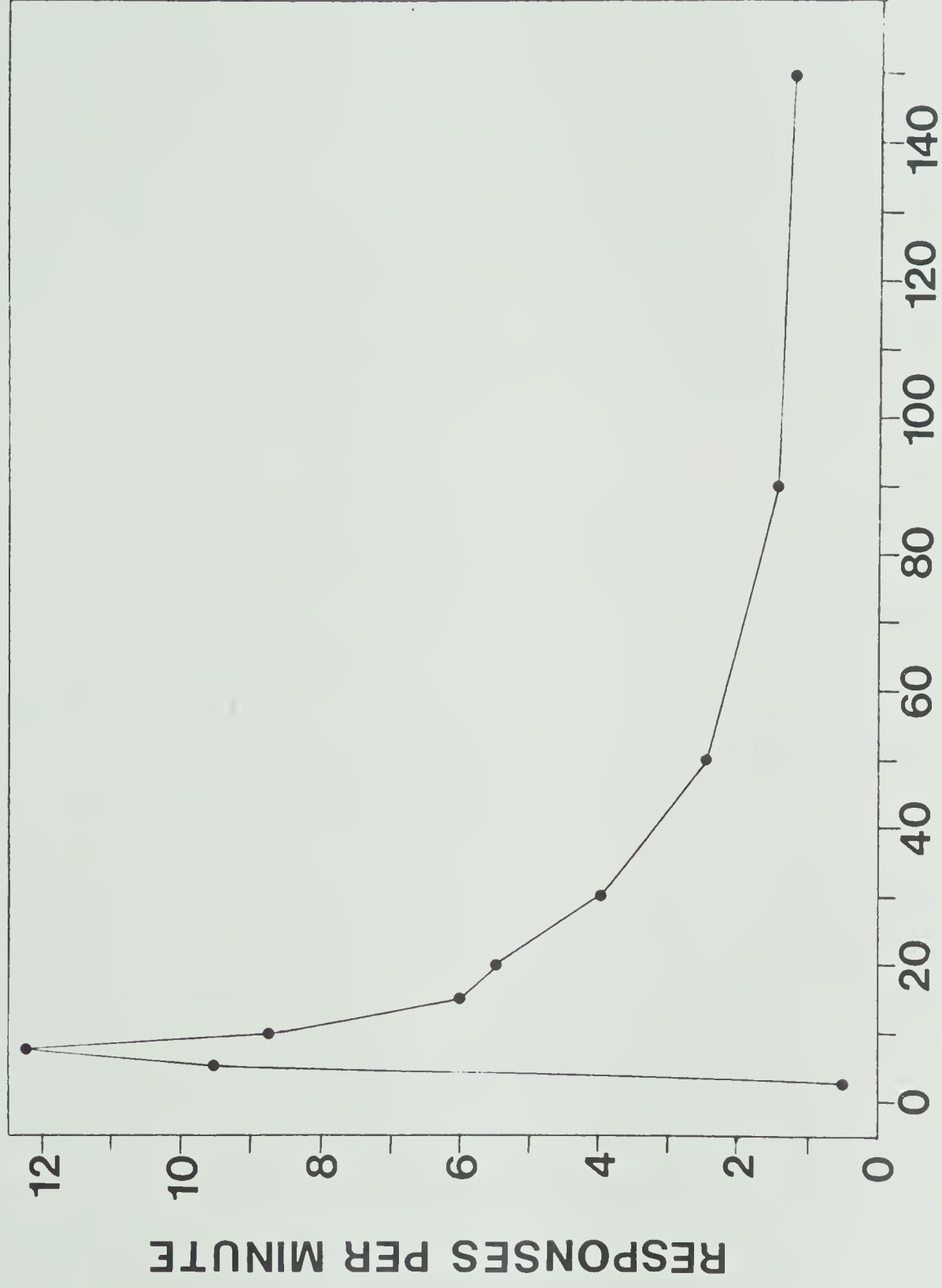
Many experiments, notably the work of Sidman (1953a; 1953b; 1958; 1962), have demonstrated that avoidance behavior can be conditioned and maintained without use of an extroceptive warning signal. In 1953(a) Sidman described an avoidance schedule in which the rat can postpone shock for a given period of time by pressing a lever. This is known as the response-shock (R*S) interval. Failure to press the lever results in shock being delivered at a regular interval; the shock-shock (S*S) interval. No extroceptive stimulus warns the animal that a shock is impending. The duration of the shock is fixed at a fraction of a second, so that the animal does not terminate the shock. Figure 2 shows the

² The following rationale for the use of this term is given by Sidman (1966) "The basic technique has been given several names, eg., nondiscriminated avoidance, the method of temporal pacing, continuous avoidance, and Sidman avoidance. The term free operant avoidance, if not self-explanatory, is more accurate descriptively than the first of these, is not as theoretically committed as the second and third, and gives a more appropriate historical credit than the last." (p.449).

Figure 2

Relation between response-shock interval and rate of avoidance responding. (Adapted from Sidman, 1960).

fig.2



RS INTERVAL IN SECONDS

relation between the R*S interval and rate of avoidance responding.

Solomon and Brush (1956) have voiced a cautionary note when one considers the avoidance phenomenon:

"We often take the avoidance phenomenon itself for granted. We somehow assume that it is natural for organisms to 'anticipate' noxious events in an 'adaptive' fashion. But it is only after we set up certain special types of environmental event sequences that the avoidance phenomena emerges".
(p. 215).

Free operant avoidance has been used extensively in the analysis of drug-behavior relationships within the last few years. Drug-rate interaction effects have been demonstrated with many classes of psychoactive "stimulant" and "depressant" drugs. Previous experiments have shown that moderate doses of drugs such as d-amphetamine (Sidman, 1956; Carlton and Didamo, 1961; Weissman, 1963; Hearst and Whalen, 1963), methamphetamine (Verhave, 1958; 1961), α -pipradrol (Bernstein and Cancro, 1962), and methylphenidate (Stretch, Blackman, and Alexander, 1966; Stretch and Skinner, 1967) facilitate avoidance behavior by producing overall increases in response rates. These effects depend partly on the parameters of a given schedule (Bernstein and Cancro,

1962; Stretch et al., 1966, 1967) and partly on shock frequency (Weissman, 1963).

Weissman found that relative and absolute increments in the rate of avoidance responding produced by 1 mg/kg i.p. of d-amphetamine were inversely correlated to a significant degree, with the baseline shock frequencies, but not with control rates of responding. Rats that received the fewest shocks during control sessions were likely to show the largest increments in responding after drug administration. The author states that:

"The present finding that the baseline shock rates are superior to the baseline response rates in predicting relative behavior changes under amphetamine suggests further that profiles derived from many measures of conditioned behavior may enable improved accuracy in the predictions of drug effects on individual subjects" (p. 297).

More recently, Stretch and Skinner (1967) using methylphenidate, made similar observations to those of Weissman. The authors found that:

"When avoidance response rates are relatively low, but accompanied by infrequent shocks, drugs such as methylphenidate or amphetamine increase the rate; however, if a comparable response

rate is associated with a greater incidence of shocks, these drugs may reduce or suppress the rate of responding" (p. 493).

Response rates may, however, be reduced by methamphetamine in an animal displaying high rates of responding immediately after shock (Verhave, 1961). Clark and Steele (1963) also found that the characteristic rate-depressant effect of chlorpromazine, when it was administered to rats working on a free operant avoidance schedule, was not found in one animal which exhibited pronounced, shock-induced bursts of responses under control conditions. The animal showed an increase in response rate under doses less than 1 mg/kg, i.m. This result was interpreted by the authors as the "differential effects of the drug upon avoidance behavior: (p. 230). They go on to state that:

"Experimental manipulation of the baseline avoidance behavior in this subject through the addition of a schedule providing for punishment of responses occurring in bursts immediately following shocks was successful in eliminating bursts of more than one or two responses: (p. 230).

A second chlorpromazine series obtained under this added punishment contingency then yielded a typical dose-effect relation for both response and shock rates

under chlorpromazine.

Dews and Morse (1961) suggest that there is a tendency, as with other classes of drugs, to consider first the possibility that the effects of the drug are dependent upon the nature of motivation - that, for example, drugs may affect behavior maintained by positive reinforcement differently from behavior maintained by use of aversive stimuli such as electric shocks. As has been repeatedly emphasized such differences are hard to establish, especially when it has been shown that the drugs cause differential effects on performance depending on the schedule of reinforcement under identical conditions of motivation. The reviewers have the impression that the stimulant effects of the amphetamines continue up to higher dose levels when performance is maintained by aversive stimuli than when it is maintained by positive reinforcement, but this has not been clearly established.

Some progress has been made in identifying other factors determining the effects of amphetamines. From the relative effects on performance on four different schedules of reinforcement of pigeons, it has been suggested (Dews, 1958b) that control rate of responding is an important factor, that sustained rates of responding are not susceptible to increase, but that very low rates or intermittent responding are readily increased. There is, of course, a limit to this relationship, in

that if tendency to respond is extremely low, ie., some minimal tendency to respond, then the output of the behavior cannot be increased by the amphetamines. This has been shown by Verhave (1958) in rats. When training in an avoidance situation had led to a substantial tendency to respond, the effects of the amphetamines became consistent in producing an increase in rate (Verhave, 1958; Teitelbaum and Derks, 1958).

The behavioral effects of methylphenidate and pipradrol seem similar to those of the amphetamines. Davis (1957) has observed that even 1 mg/kg methylphenidate produced a large decrease in activity in already hyperactive monkeys, a finding further emphasizing the dependence of this type of effect on the on-going behavior.

STATEMENT OF THE PROBLEM

The interpretations of the net behavioral effects of various drugs, as outlined previously, are very complex. Many, oftentimes seemingly trivial, factors must be placed under strictest control before, even minimal, generalizations can be accurately set forth.

Due to the dissimilarity of the various measures used (ie. positive vs. negative reinforcement) the broader generality of drug-behavior hypotheses has been

considerably hampered. The large majority of operant conditioning experiments utilizing stimulant drugs have been carried out with the amphetamines (Dews, 1958b; Verhave, 1961; Weissman, 1963); although, more recently, other stimulant drugs such as α -pipradrol (Bernstein and Cancro, 1961) and methylphenidate (Stretch et al, 1966; Stretch and Skinner, 1967) have been utilized.

Dews (1958b), using positive reinforcement, proposed that the behavioral effects of drugs such as the amphetamines are determined largely by the frequency of the responses being studied. If the response rate is low, such drugs increase the rate; but when responses under control conditions occur frequently, amphetamine decreases the overall rate.

In the light of present knowledge of drug-rate interaction effects, two important questions can be appropriately raised at this point: a) do drugs such as methylphenidate and α -pipradrol have similar behavioral effects as those observed with the amphetamines, and b) does Dews' drug-rate hypothesis, as outlined above, hold for the aversive case, ie. using negative reinforcement?

Weissman (1963), as seen previously suggests that, using avoidance measures, shock frequency plays a more important role as a determinant of drug-rate interaction

effects. Stretch and Skinner (1967) offer strong support to Weissman's observations. A further investigation by Bernstein and Cancro (1962) has pointed to the importance of the temporal variables of avoidance conditioning on drug-behavior interaction. The authors in conclusion, suggest that:

"The results of this experiment seem to indicate that not only are drug-behavior interactions a function of the particular schedule under which the behavior is being maintained but that such differences may also be observed when the parameters governing the behavior within a single schedule are altered" (p. 113).

It is increasingly apparent that the drug-induced changes in avoidance response rates cannot be interpreted solely in terms of a specific rate interaction effect (Cook and Catania, 1964). Taking into account those observations of Weissman (1963) and Stretch and Skinner (1967), the role of shock frequency in the investigation of drug-behavior interactions in free operant avoidance, cannot be underestimated. Does the change in baseline response rates occur as a direct result of drug-induced responding; or does the drug alter the patterning of shocks within the schedule, which in turn manifest itself in the observed avoidance rate changes? This question is

pertinent to the aims of the present investigation.

With these bases the present investigation was designed to determine whether Dews' drug-rate interaction hypothesis can be applied to behavior maintained by aversive stimulation when shock frequency is more adequately controlled, through a yoked control design (Church, 1964), than in previous investigations.

In more conventional yoked control experiments (Ferster and Skinner, 1957; Church, 1964) the design involves a number of subjects that are paired on some basis. One of the two members of each pair is randomly selected as the experimental subject ; the other member is the control subject. The experimental subject is put into an instrumental learning situation in which an event occurs if it makes a particular response; the control subject is put into a situation in which an equivalent event occurs if its yoked experimental subject makes the response. Church states that:

"That critical characteristic of this design is that an experimental subject determines the presentation of events to its control subject so that the experimental and control subjects receive the same number and temporal distribution of events" (p. 122).

JUSTIFYING THE TECHNIQUE

Within the framework of the problems previously stated the present investigation was designed to:

- 1.) ascertain the broader generality of Dews' drug-rate hypothesis (as stated above), to behavior maintained by aversive stimulation, using methylphenidate, and
- 2.) more thoroughly define the drug-rate, shock-rate interaction effects, by controlling the shock frequency to a more adequate degree, than in previous experiments.

To investigate the first consideration, it was necessary to procedurally incorporate a fixed ratio schedule into the free operant avoidance paradigm. Fixed ratio avoidance, that is where the animal must make a fixed number of responses to postpone shock is not directly comparable to a fixed ratio schedule employing positive reinforcement. Most obvious is the fact that a positively reinforced ratio schedule does not have temporal parameters, as is the case with ratio avoidance. A more comparable positively reinforced schedule would be the differential reinforcement of a high rate (drh) in which the animal not only has a ratio requirement to fulfill but a specified interval of time in which to complete it. Under these scheduling conditions extremely high response rates (depending upon the values of the R^*S ,

S*S parameters)³ are produced.

Fixed ratio avoidance, in isolation, was first described by Verhave (1959) who employed a ratio requirement of eight, generating successful ratio avoidance in a number of rats. During this investigation, Verhave manipulated the R*S parameter and ascertained its effect on response rate. The initial parameters of Verhave's schedule were R*S=S*S=30 secs. with an FR=8. Then by increasing and decreasing the length of the R*S interval through a range of 300 to 15 seconds, he was able to produce correspondingly substantial increases in response rate⁴ (See Figure 3). Verhave, noting Sidman's results (Sidman, 1953b), points out "that at R*S>90 sec. the rate of responding drops to a very low level [so that] in some animals a stable rate cannot be maintained" (p. 960). However, Verhave, by using a fixed ratio, showed that responding can be stabilized at R*S=300 seconds.

The procedure adopted in the second consideration

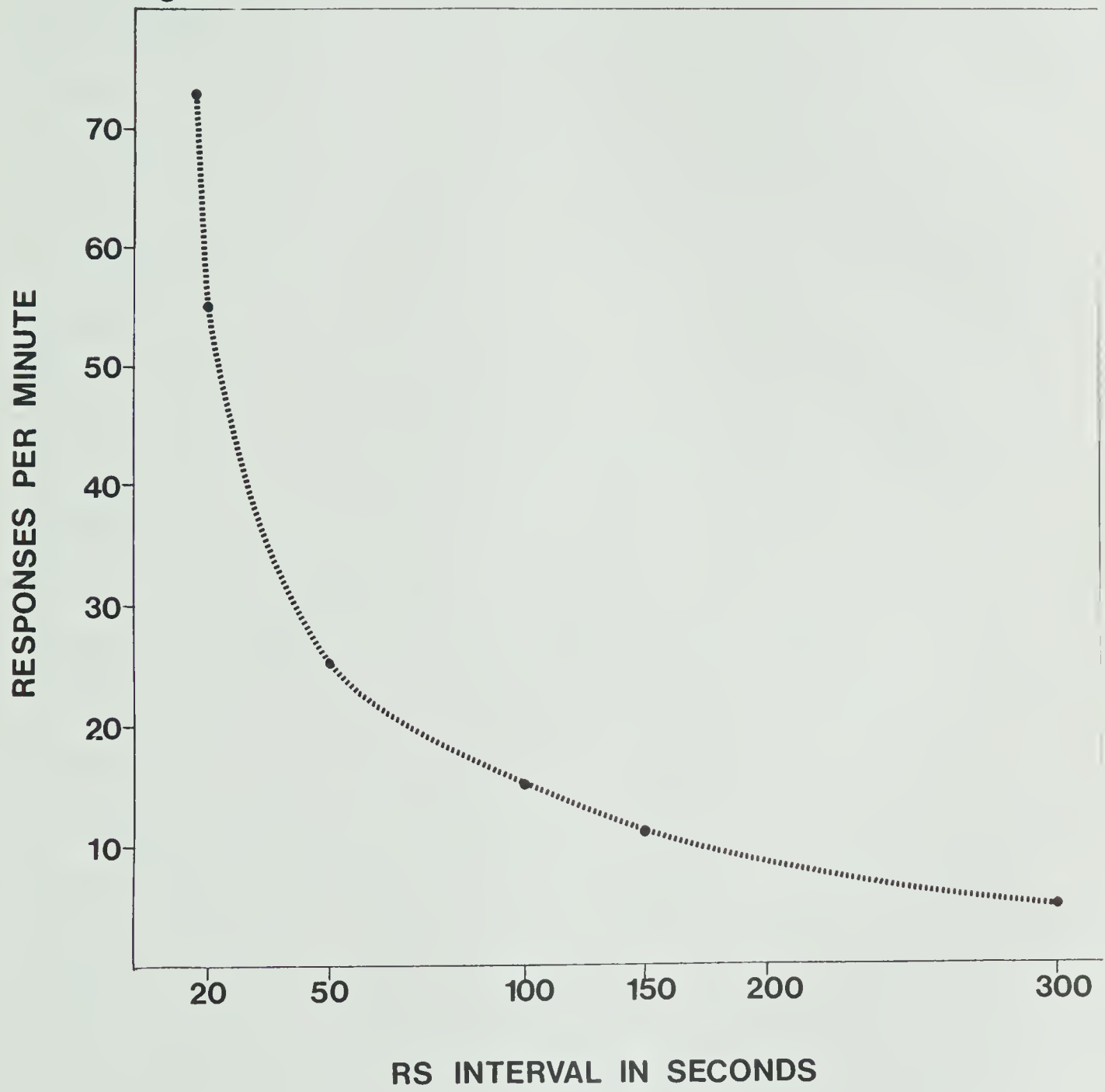
³ Holding the S*S interval constant (eg 5 secs) the response rate increases with a decrease in the value of the R*S interval; so that, eg. R*S 20" S*S 5" engenders a much higher baseline rate than R*S 80" S*S 5".

⁴ The rate of responding as a logarithmic function of the R*S interval was fitted by the method of least squares $y = 157.38 + 0.1588x - 79.84 \log x$ in which y = rate of responding in minutes and x = duration of the R*S interval in seconds.

Figure 3

Rate of avoidance responding as a function of the R*S interval. (Adapted from Verhave, 1959).

fig. 3





involved a modification of the "yoked control" design (Church, 1964) as mentioned in the previous section. Once the animals had achieved a stable baseline fixed ratio avoidance rate they were paired-off depending upon the similarity of their mean response and shock rates. (See Method section following for details). Each pair consisted of one high rate (R*S 20") animal and one low rate (R*S 80") animal. Since the high and low response rates of animals within a pair have different shock frequencies maintaining their behavior it was necessary to employ a period during the experimental session in which the animals would be "yoked" together receiving common shock frequency. The modification of the conventional yoked control design developed, involved a variable interval 'free' (unavoidable) shock presentation common to both animals of the pair. This was operative, on random days, during the third period of the experimental sessions.

Maintenance of operant response rates by unavoidable shocks was first demonstrated by Sidman, Herrnstein and Conrad in 1957; subsequently demonstrated by Waller and Waller, (1963), and Kelleher, Riddle and Cook (1963). Sidman et al (1957) found that a pre-aversive stimulus could increase responding when a continuous shock avoidance schedule (Sidman, 1953) was used to maintain behavior; with further exposure to this procedure, however, the

response rate during the pre-aversive stimulus gradually decreased toward the response rate that prevailed between presentations of the pre-aversive stimulus.

A study by Boren and Sidman (1957) amply attests to the difficulty in interpreting the rate of shock frequency in free operant avoidance. The authors investigated the effects of varying the probability that shock will actually occur when the animal fails to emit the avoidance response. "It was found that the rate of avoidance responding remained essentially constant from 100 percent to 30 percent shock" (P. 192) at lower shock percentages, however, the authors found that the response rate dropped sharply.

These considerations, then, constitute the basis for justifying the technique employed in the present experiment.

PHARMACOLOGY OF METHYLPHENIDATE

Specific modification of the structures of certain phenylisopropylamines with central stimulant effects has given rise to a group of pharmacologically active agents which are derivatives of 2-benzylpiperidine. One therapeutically useful member of this group is methyl α -phenyl-2-piperidineacetate, known more commonly as methylpehnidate hydrochloride, or Ritalin.

i) CENTRAL STIMULANT ACTIVITY

The clinical utility of methylphenidate lies in its ability to increase central nervous activity without adversely influencing the cardiovascular system or appetite. The degree of central stimulant activity of the drug lies between the lower and upper limits represented by caffeine and amphetamine respectively [Meier, Gross and Tripod (1954); Kruger and McGrath (1964)].

The first descriptive summary of the effect of methylphenidate was by Meier et al (1954). They showed that parenteral or oral administration of the drug to mice, rats, rabbits, and dogs results in increased coordinated motor activity. It was expressed in the experimental animals, as a general restlessness, and particularly, as a coordinated increase in motility; a tendency to move about and run, also to eat or gnaw, without becoming aggressive. Depending on the animal, the species and mode of administration, this central stimulating effect appears after doses of 0.5 to 1.5 mg. per kg., lasts for several hours and then subsides, leaving signs of fatigue. Larger doses of methylphenidate produce an atactic gait and clonic tonic convulsions. Garberg and Sandberg, (1960) showed that methylphenidate is about one seventh as potent as d-amphetamine in increasing motor activity

in rats to three times control activity.

In the "social situation" in which mice are grouped five to a container of standard dimensions, methylphenidate, like amphetamine (Chance, 1946) is more toxic (Greenblatt and Osterberg, 1961). The toxicity is increased to a slightly lower degree than is that of amphetamine. This work showed a correlation between increased lethality and the increase in motor activity and rectal temperature induced by the drugs.

ii) EFFECTS ON SCHEDULE-CONTROLLED BEHAVIOR

Methylphenidate has been used more recently on schedule-controlled operant behavior. Instances of its use in both positive and negative reinforcement have been recorded.

In the vein of positive reinforcement Mendelson and Bindra (1962) have shown that methylphenidate in rats will depress the rate of bar pressing for a water reinforcer. The authors attribute this effect to the disorientation brought about by the increased general activity caused by the drug. Stretch and Dalrymple (1968) however, also using a water reinforcer, found that rats responding at a low rate on a DRL schedule of reinforcement increased their response rates, over control rates, under all dose levels

(2.5, 5.0 and 10.0 mg/kg) administered. The difference in findings would be attributable to the differential effects of the drug on the different schedule parameters governing the on-going behavior.

Rate-dependent effects of methylphenidate in rats were demonstrated by Mechner and Latranyi (1963). The authors found in this study that it was possible to distinguish three close-related psychomotor stimulants, caffeine, methamphetamine, and methylphenidate by means of two operant procedures, fixed interval (FI 30 sec.) and fixed ratio (FR 45). Under the fixed interval schedule, the subject was required to manipulate two bars; a response on bar A initiating a 30 second fixed interval and the first response on bar B following the end of this interval being reinforced. Typically, the subject paused after starting the interval, then began to respond on bar B, the response rate gradually accelerating until a reinforcement was obtained. It was immediately evident from the results, that in spite of wide individual differences, administration of each of the drugs resulted in an increase in the number of responses to bar B. However, caffeine was much less effective in this respect than methamphetamine and methylphenidate and this difference was shown to be statistically highly significant. Further, at higher

dosages of 12 and 24 mg/kg, caffeine did not produce destruction of the temporal discrimination as did the remaining two drugs.

When the subject was required to perform under the fixed ratio schedule, it was again presented with two levers. 46 responses to bar A were required before a response to bar B would be reinforced. As in the fixed interval procedure, premature responses to bar B did not reset the count, but were also not reinforced. The subject typically completed a large number of the bar A responses before making a bar B response which was usually premature. Following the first bar B response, the subject normally alternated between A and B until the reinforcement was obtained, with an increasing number of bar B responses as the end of the ratio requirement approached. A post reinforcement pause was normally observed and again, wide individual differences were apparent. All three drugs increased the number of responses to bar B, but in this case, the effect was less marked under methamphetamine than with caffeine or methylphenidate. The three drugs were thus quite clearly distinguished; fixed interval isolates the caffeine effect, and fixed ratio, methamphetamine.

At the peak of its dose response curve, methyl-

phenidate had behavioral effects very similar to methamphetamine under the fixed interval schedule and behavioral effects similar to those of caffeine under fixed ratio.

The use of methylphenidate on free operant avoidance was cited previously.

iii) MECHANISMS OF ACTIVITY

The exact mechanism of the CNS stimulant activity of methylphenidate remains to be clarified. The available information suggests a stimulating effect on the brain stem reticular formation. Cole and Glees (1956) have proposed that methylphenidate acts through hypothalamic sympathetic activity either by removal of an inhibitory influence on sympathetic centers or by direct stimulation of these areas. Maxwell et al (1959) have suggested that methylphenidate acts directly on the receptor site to alter responsiveness in some manner. Studies by the same author on the acutely and chronically denervated nictating membrane suggest that part of the activity of methylphenidate may be dependent upon the presence of catecholamines, since the acutely denervated membrane was more responsive to methylphenidate than was the chronically denervated tissue. These data seem to show that no massive release of catechol-

amines into the general circulation follows the administration of methylphenidate, but these substances may have to be present for an effect of the drug to occur.

METHOD

SUBJECTS

Seven hooded female rats designated HF11, HF8, HF7, HF6, HF9, HF3, HF4, respectively, of the McGill University - Royal Victoria Hospital strain, bred in the laboratory, approximately four months old, served as subjects in this investigation. Each animal received unrestricted access to food and water except during experimental sessions.

APPARATUS

The experimental apparatus consisted of two, identical, Grason-Stadler Model E3125AA animal chests. Since the chests were identical, description of a single chest will be given. Each chest was equipped with a wall mounted lever and grid floor. A dim red house light was on continuously during the experimental sessions. Shock of 3.0 milliamp intensity and 0.5 second duration was delivered through the grid floor by a Grason-Stadler Model E1064GS shock generator. Shock was scrambled so that the polarity of the grid floor reversed randomly and rapidly. The experimental contingencies were programmed by automatic electro-mechanical equipment, with provision for an adjustable setting of the R*S parameter. A Gerbrands cumulative

recorder continuously monitored avoidance responding and digital counters totalled the responses and shocks for each forty minutes of the 200 minutes session. Control equipment was located in an adjacent room to the test chambers.

PROCEDURE

The first step in the acquisition of free operant avoidance is the 'shaping' procedure. Since this is the same for each animal a detailed description of shaping for one animal will suffice. The first ten minutes of the first experimental session was allotted as an exploration-habituating period. The rat was allowed to move freely, to explore the chamber, and become habituated to the experimental environment, in the presence of a dim red light. The automatic programming equipment was then turned on and shock, of 1.0 milliamp intensity¹ and .5 sec. duration was delivered every five seconds in the absence of a lever press. Once the rat had taken a limited number of shocks (10 to 15 shocks) the shaping procedure was begun. The first behavior to be selectively reinforced, that is, inter-

¹

Initial intensity of the aversive stimuli is of the utmost importance. Responding is often suppressed if the initial intensity of the aversive stimulus is too great.

ruption of the shock sequence, was movement of the rat into the area of the test chamber where the lever was located. Rearing behavior was then selectively reinforced in order to increase the probability that the rat would strike the lever fortuitously². Any lever presses were reinforced and the shaping procedure was discontinued when the animal displayed a consistent pattern of "pseudo-avoidance"³. Time-to-acquisition varied between animals ranging from fifteen minutes to one hour. (See Figure 4).

Following successful acquisition of the lever press, a free operant avoidance schedule (Sidman 1953a) with a response-shock interval of 20 seconds and a shock-shock interval of 5 seconds was operative for 25 sessions, each of two hundred minutes duration⁴. Responses and shocks were recorded on each of five forty minute intervals comprising the two hundred minute experimental session. (See Figure 5).

It is appropriate, at this point, to develop the schedule differences between free operant avoidance

² This procedure is known as reinforcing successive approximations to the lever press.

³ Shock -elicited responding on the lever.

⁴ Shock intensity was increased to 2.0 ma for the free-operant avoidance.

Figure 4

Acquisition of free operant avoidance showing complete session. Oblique pips denote shocks.

Rat HF11.

Figure 5

R*S 20 S*S 5 FR 1 avoidance parameters showing complete session. Oblique pips denote shocks.

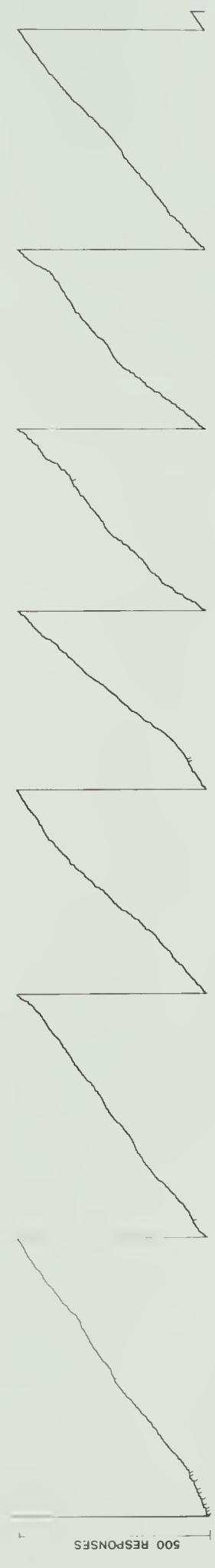
Rat HF8.

HF11 ACQUISITION



40 MINUTES

HF8 R*S20 S*S5 FR1



and free operant ratio avoidance. Under conventional free operant avoidance parameters the animal is required to make a single response within the R*S interval in order to postpone the onset of a noxious stimulus (eg. shock). However, under ratio avoidance parameters, the condition to postpone shock is quite different. The animal must now make a set number (fixed ratio) or an average number (variable ratio) of responses within the R*S interval to postpone the occurrence of a shock. In the fixed ratio paradigm, if the animal does not complete the ratio requirement within the R*S interval, a shock occurs which immediately erases the prior responses made in that interval; the animal now has to complete the ratio requirement anew within the S*S interval in order to escape from the shock. As will be seen in the Result Section following, this leads to a rather high frequency of shocks during the first several minutes of the experimental session, particularly with the R*S 80 sec. animals.

After the animals had stabilized on 25 sessions of R*S 20 S*S 5 FR 1, the number of responses required for shock avoidance was gradually increased until a stable fixed ratio 5 was achieved. This was

carried out in the following manner:

FR2	2 sessions	(2.0 ma shock)
FR2 to FR3	2 sessions	"
FR3	6 sessions	"
FR3 to FR4	2 sessions	(Shock increased to 3.0 ma) ⁵
FR4	4 sessions	(3.0 ma shock)
FR4 to FR5	1 session	"
FR5	30 sessions	"

Stability was assessed by means of the criterion employed by Schoenfeld, Cumming and Hearst (1956) and is described by them as follows:

"The first seven days on any schedule are not considered in computing stability. For the next six days, the mean response rate per minute of the first three days of the six is compared with that of the last three days; if the difference between these means is less than 5% of the six days' mean, the animal is considered to have stabilized. If the difference between the sub-means is greater than 5 percent of the grand mean, another experimental day is added and

⁵

Boren, Sidman and Herrnstein (1959) have shown that the rate of avoidance responding increases, to an asymptote, as the shock intensity is increased to a maximum of 3.0 to 3.2 ma; after which no further increase in responding is obtained.

similar calculations are made for that day and the 5 days immediately preceeding it. The process is continued until the criterion is met." (P. 567). It should be noted that the authors in the 1956 paper and subsequently Cumming and Schoenfeld (1960), reported that the criterion was not entirely satisfactory, since fluctuations beyond the 5 percent limit were noted in a number of subjects after they had met the criterion. However, as Dalrymple (1966) has noted, "it is the only method other than visual inspection of cumulative records, that offers any indication of the subject's approach to stability" (P. 41), and was employed in the present study⁶.

Once the behavioral baseline was established for all animals at R*S 20 S*S 5 FR 5, parameter changes of the R*S interval were programmed in the following manner:

(1) Three animals (HF11, HF7 and HF6) remained on R*S 20 S*S 5 FR 5 establishing a high baseline response rate.

(2) Three animals (HF3, HF8 and HF9) were subjected to increases in the R*S interval according to

⁶

A full discussion of the problems associated with behavioral stability and stability criteria is offered in "Tactics of Scientific Research" by Murray Sidman (1960).

the scheme below:

R*S 60	S*S 5	FR 5	5 sessions
R*S 80	S*S 5	FR 5	10 sessions

The response rate engendered by this manipulation was reduced to the order of one third that established on the R*S 20 parameters (Sidman, 1953b; Verhave, 1959).

Once stable response rates were obtained in the high rate (R*S 20) and low rate (R*S 80) animals, drug tests were made to determine whether methylphenidate⁷ affected the differential rates of avoidance responding. Dosages of methylphenidate (4, 8, and 16 mg/kg) were administered in an essentially random sequence. The effects of each dosage, given intraperitoneally, were determined on four separate occasions, interspersed with control sessions and sessions preceded by injections of saline solution. Throughout this series of drug tests the injections were administered a minute before the beginning of the experimental session. Thirty-eight sessions were required to complete drug tests.

The next phase of the investigation, in order to ascertain more effectively the role of shock frequency in drug-rate interaction effect, required the design

⁷ The lyophilized hydrochloride salt of this drug dissolved in distilled water.

of a modified yoked control (Church, 1964) procedure; as mentioned previously in the introduction. This required a number of changes in the basic procedure. First, the animals were paired so that each pair consisted of one "high rate"⁸ (R*S 20) animal and one "low rate" (R*S 80) animal, depending upon the similarity of their mean shock frequencies during the third 40 min. period of the five 40 min. periods comprising the session. Second, the automatic programming which had consisted of five 40 min. periods of ratio avoidance, was now modified in the following manner: A two minute time-out, in which the experimental contingencies were not operative, followed each successive 40 min. period. During the third 40 min. period a variable interval (V.I.) tape (constructed on the mean shock rate per minute for each pair) became operative, delivering common shock to both animals during this period (ie yoked V.I. shock presentation). Responses occurring during this period were not effective in postponing the programmed shocks (unavoidable shock). The overall V.I. session, then, was as follows: ratio

⁸

Response rates engendered by the R*S 20 parameter were approximately 32.00 responses per minute as compared to the rate engendered by the R*S 80 parameter which was approximately 8.00 responses per minute. These have been termed, therefore, the high rate (R*S 20) and low rate (R*S 80) animals, respectively.

avoidance for 40 minutes, 2 minute time-out, ratio avoidance for 40 minutes, 2 minute time-out, variable interval shock presentation for 40 minutes, 2 minute time-out, ratio avoidance for 40 minutes, 2 minute time-out, ratio avoidance for 40 minutes, 2 minute time-out, and end of session. A session which involved the V.I. period was termed a V.I. Session, and a session which consisted entirely of periods of ratio avoidance was termed a Ratio Session. Each pair of animals received ten V.I. sessions at random, interspersed with ten Ratio sessions.

- | | |
|------------------|-------------------|
| 1. V.I. session | 11. Ratio session |
| 2. Ratio session | 12. V.I. session |
| 3. V.I. " | 13. Ratio " |
| 4. Ratio " | 14. V.I. " |
| 5. Ratio " | 15. V.I. " |
| 6. Ratio " | 16. Ratio " |
| 7. V.I. " | 17. V.I. " |
| 8. V.I. " | 18. Ratio " |
| 9. V.I. " | 19. Ratio " |
| 10. Ratio " | 20. V.I. " |

When re-stabilization had been achieved a second series of drug tests was begun. This series differed from the previous one in the following respects:

1) dosages of methylphenidate were now 4, 8 and 12 mg/kg and 2) throughout this series of determinations, the injections were administered during the 2 minute time-out between the second the third 40 min. periods of the session. This procedure allowed for two critical observations: First, the drug was maximally effective during the V.I. period or the Ratio period depending upon which type of session was programmed. Second, the drug was effective upon stable avoidance behavior and not interacting with the shock-induced escape responding⁹ at the beginning of the experimental session. The effects of each dosage, given intraperitoneally, were determined on four separate occasions under both V.I. and Ratio sessions, interspersed with V.I. and Ratio control sessions and sessions of

⁹ In many animals at the beginning of the experimental session responding does not occur until a series of shocks has been delivered. Two things may result from this: First, the animal may press the lever immediately and hold it down, so that shock is postponed briefly but will reoccur within seconds if another response is not forthcoming, or, secondly, following a shock the animal may emit several responses on the lever in rapid succession. This phenomenon is known as pseudo-avoidance, shock-elicited responding or adventitiously reinforced escape behavior (Keehn and Chaudrey, 1964). Such behavior is observed invariably at the outset of each experimental session but, in general, persists no longer than 10 to 15 minutes and is not characteristic of the patterns of responding observed subsequently during the remainder of the session.

both preceded by injections of saline solution. Each animal, therefore, received:

4 Ratio control sessions	-	4 V.I. control sessions
4 " saline "	-	4 " saline "
4 " 4 mg/kg "	-	4 " 4 mg/kg "
4 " 8 mg/kg "	-	4 " 8 mg/kg "
4 " 12 mg/kg "	-	4 " 12 mg/kg "

These ten different conditions were operative in an essentially random sequence with two drug days never occurring in succession.

For this phase of the investigation which entailed yoked pairs of animals for V.I. shock presentation, a change of subjects was carried out. During the first series of drug determinations two of the R*S 80 sec. animals (HF3 and HF9) encountered serious difficulties with the fixed ratio avoidance schedule. Rat HF9 died during one experimental session under 16 mg/kg drug dosage; animals HF6 (R*S 20) and HF3 (R*S 80) displayed increasingly persistent patterns of pseudo-avoidance responding and since they encountered problems under the drug conditions, were deemed unreliable and dropped from the experiment. Rat HF4 replaced HF9 and was paired with HF7 an R*S 20 sec. animal. Experimental arrangements for each subject are summarized below.

SUBJECTS AND PARAMETERS

Series 1

Rat:	HF11			
	HF7	R*S 20	S*S 5	FR 5
	HF6			

	HF8			
	HF3	R*S 80	S*S 5	FR 5
(Died)	HF9			

Series 2

Rat:	HF11	R*S 20	S*S 5	FR 5/VI 4 mins.
	HF8	R*S 80	S*S 5	FR 5/VI 4 mins.

Series 3¹⁰

Rat:	HF7	R*S 20	S*S 5	VR 5/VI 2 mins.
	HF4	R*S 80	S*S 5	VR 5/VI 2 mins.

¹⁰

Rats HF7 and HF4 initially began the second series of drug determinations. However, under the FR 5 avoidance requirement, both subjects showed a rather large degree of variability in their control baselines. This was particularly manifest in rat HF4 who displayed an extremely fluctuating shock frequency (See Figures 35 and 36) under FR control conditions. Both subjects showed stable baseline response rates under variable interval 2 min. shock presentation. As a consequence of the unstable FR behavior a further schedule change

Footnote ¹⁰ (continued)

was made. Avoidance baselines were reestablished for both subjects on a variable ratio rather than the fixed ratio avoidance schedule. Variable ratio differs from fixed ratio avoidance in that the subjects now have to make, on average, five responses during the R*S interval to postpone the onset of shock.

The results to be presented in this section were derived from the consecutive phases of the experiment, as follows: (i) establishment of fixed ratio avoidance behavior; (ii) findings emerging from the first series of drug determinations; (iii) paired fixed ratio/variable interval restabilization; (iv) findings emerging from the second series of drug determinations; (v) paired variable ratio/variable interval restabilization; and (vi) findings emerging from the third series of drug determinations.

(i) Establishment of fixed ratio avoidance behavior.

During this first phase of the experiment, once the animals had acquired the avoidance response, each animal was given 25 sessions of R*S 20 S*S 5 FR 1 avoidance. Examples of the performance engendered by these parameters are shown in Figures 6, 7, 8 and 9. Overall rates of responding are consistent, while day to day fluctuation, within acceptable limits, is evident (Figures 6 and 8). The average number of shocks occurring per hour (Figures 7 and 9) also fluctuates from session to session over the 25 consecutive sessions. Individual differences in the acquisition of the free operant avoidance schedule were observed; as an example,

Figure 6

Avoidance baseline, R*S 20 S*S 5 FR 1, overall response rate per minute for 25 consecutive sessions. Rat HF7.

Figure 7

Avoidance baseline, R*S 20 S*S 5 FR 1, average shock rate per hour for 25 consecutive sessions. Rat HF7.

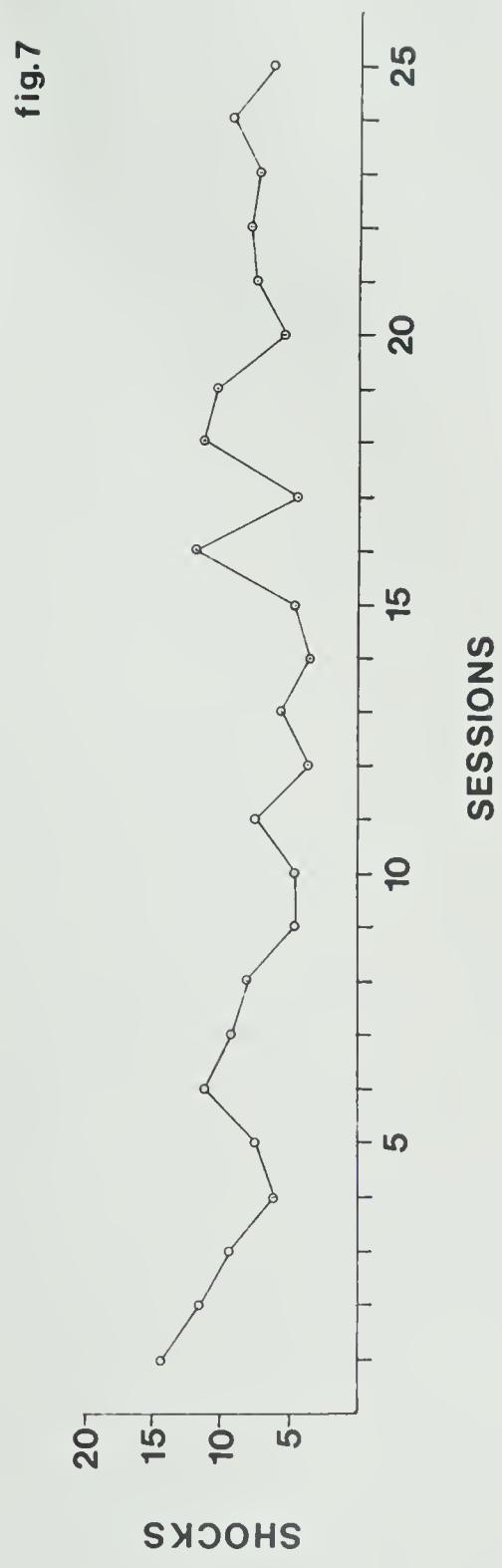
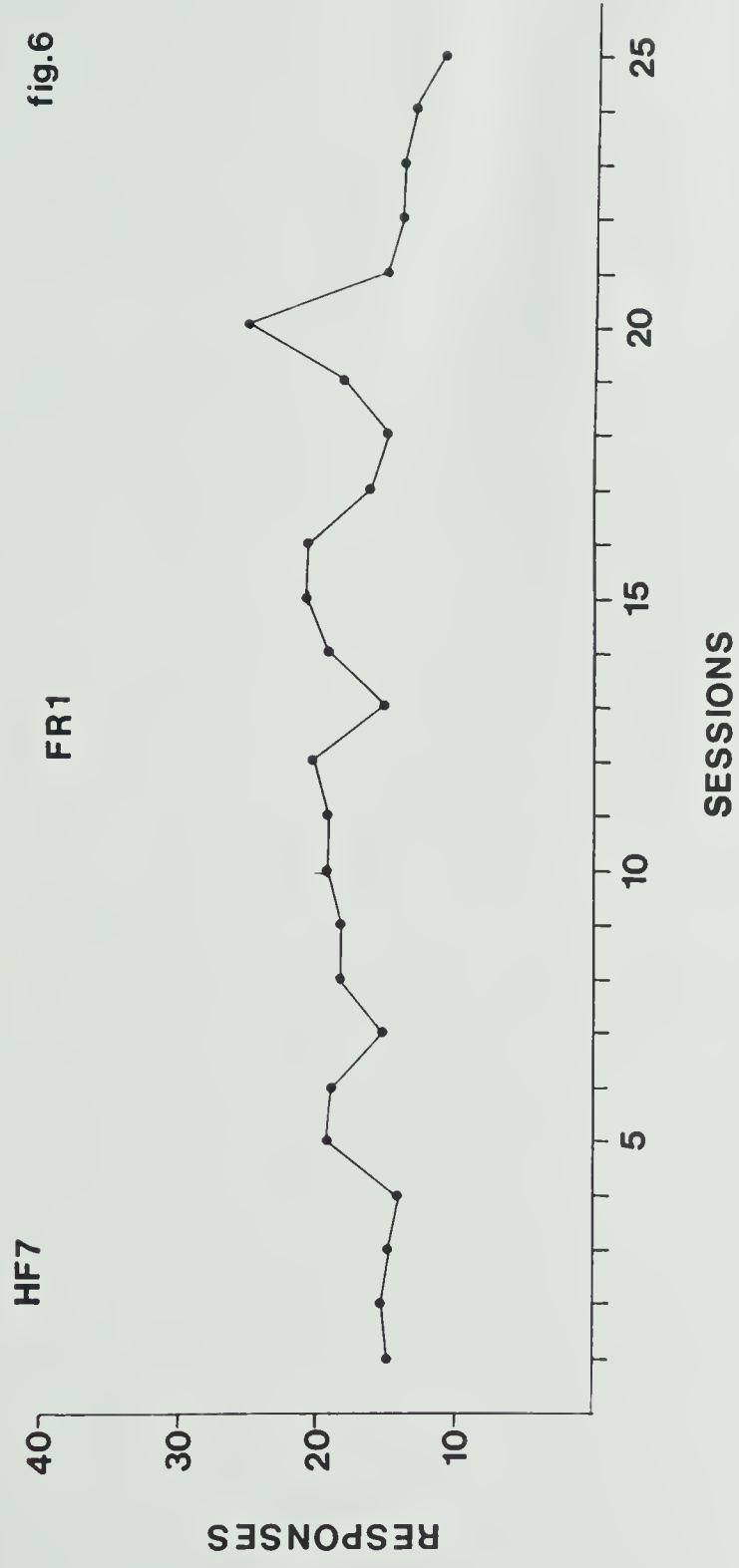


Figure 8

Avoidance baseline, R*S 20 S*S 5 FR 1, overall response rate per minute for 25 consecutive sessions. Rat HF4.

Figure 9

Avoidance baseline, R*S 20 S*S 5 FR 1, average shock rate per hour for 25 consecutive sessions. Rat HF4.

the overall response rate of rat HF4 (Figure 8) is considerably less than that of HF7 (Figure 6). Also evident is the accompanying higher shock frequency occurring per hour for HF4 (Figure 9). This intersubject variability was observed consistently throughout the experiment. Within 25 sessions all animals had satisfied the stability criterion, however, as assessed by the method of Schoenfeld, Cumming and Hearst and described previously in the Method section.

Figures 10 and 11 exemplify the typical results of increasing the number of responses required to avoid shock from two (FR2) to five (FR5). An overall increase in response rate is observed with an apparent greatly-increasing shock frequency. Closer examination of the data reveals that the average shock rate per period, over a 5 period session, is not as high as it appears in Figures 10 and 11. The shock rate that does increase significantly with an increase of the ratio requirement is that for the first 40 minute period of the session. This is the warm-up effect that persisted in all subjects throughout the experiment. Figure 12 shows the change in shock rate as the experimental session progresses. There is generally observed a decrease in shocks through each 40 minute period to some minimal value by the fourth period after which it remains fairly

Figure 10

Transition from FR 2 to FR 5, overall response rate per minute (solid line) and average shock rate per hour (dotted line) for 31 consecutive sessions. Rat HF7.

HF7

fig.10

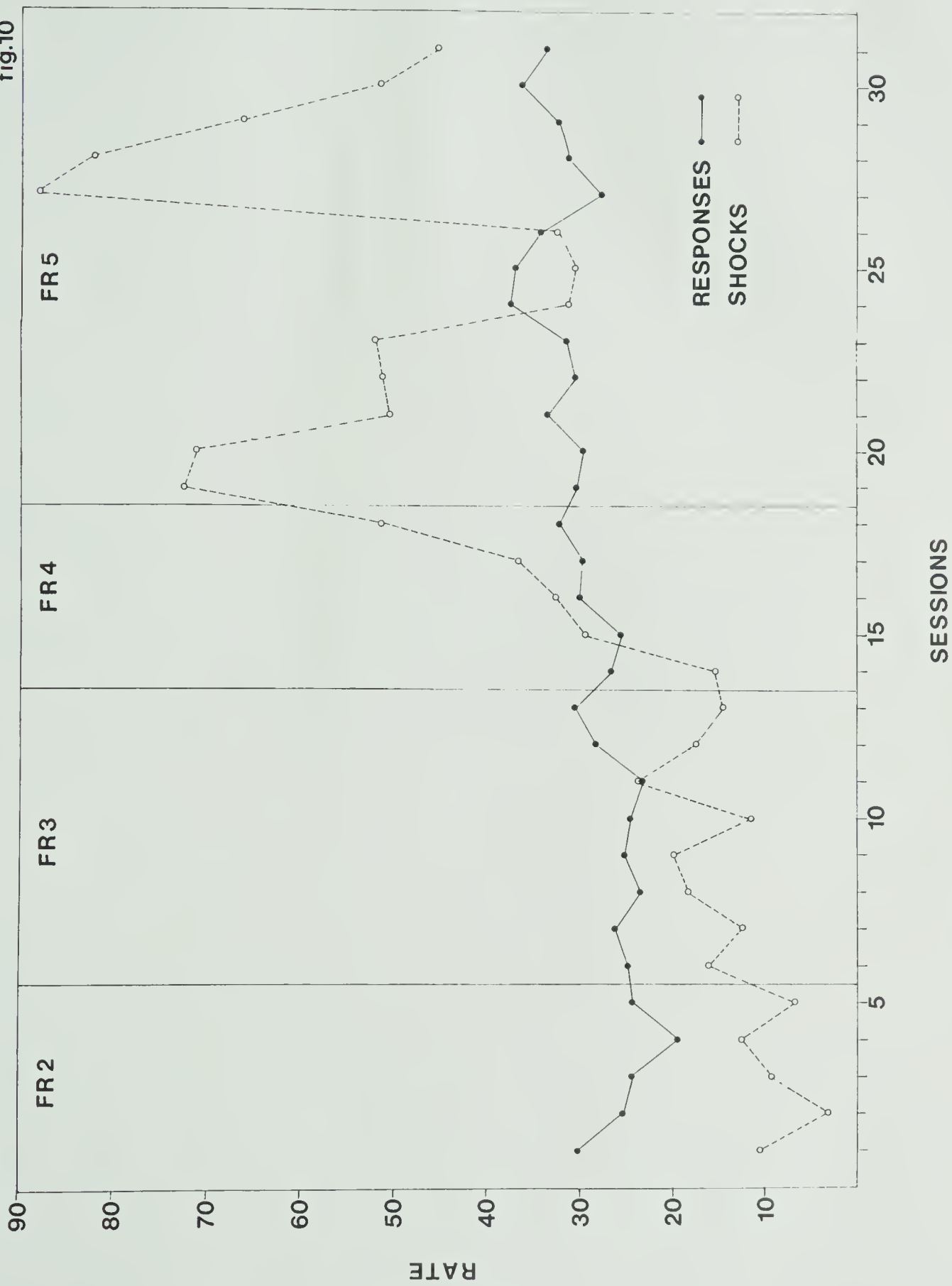


Figure 11

Transition from FR 2 to FR 5, overall response rate per minute (solid line) and average shock rate per hour (dotted line) for 31 consecutive sessions. Rat HF8.

HF 8

fig.11

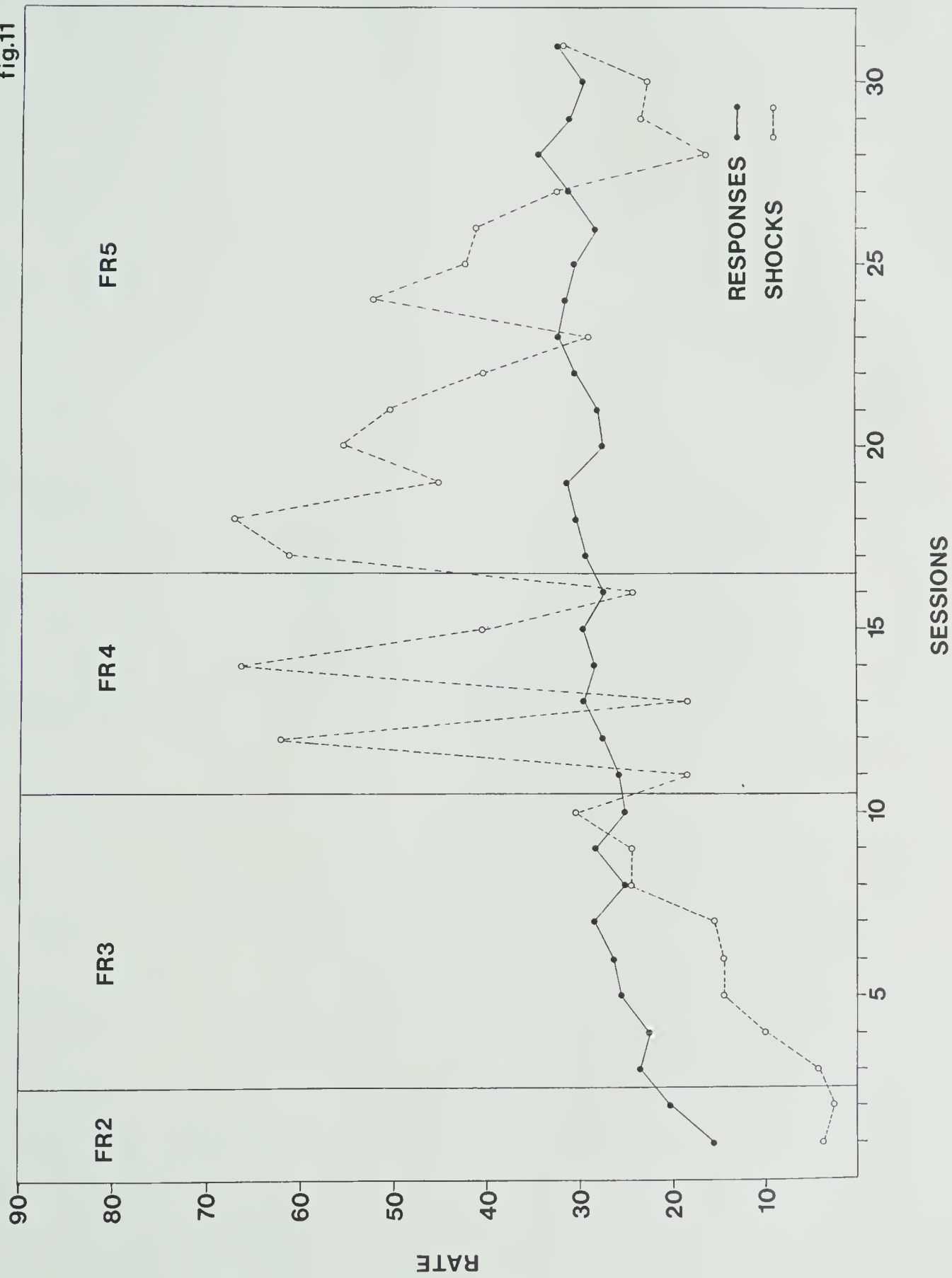
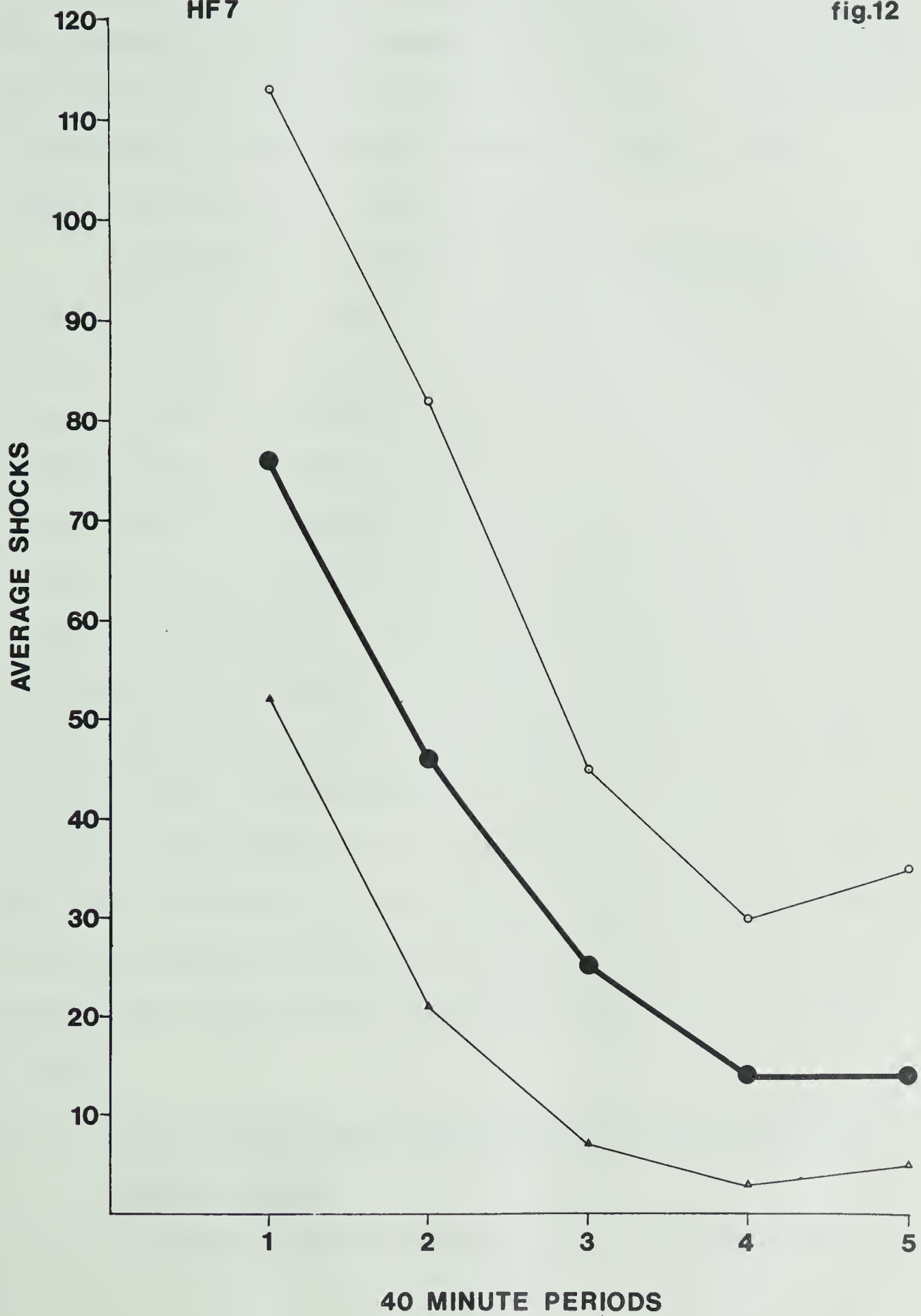


Figure 12

Average number of shocks occurring per period over 10 experimental sessions on FR 5 avoidance. Maximum shocks (open circles) and minimum shocks (open triangles) are also shown. Rat HF7.

HF 7

fig.12



constant for the remainder of the session. The cumulative records in Figure 13 demonstrate the rate changes and changes in shock frequency as a function of increasing the ratio requirement from one to five. Particularly evident is the extended 'warm-up' effect at the higher ratio values. (FR 3,4, and 5).

A representative result of the parameter manipulation of the R*S interval is shown in Figure 14. The overall response rate per minute decreased with an increase in the R*S interval value to low levels of responding which differed for each of the three animals. (See Table 1, in appendices). Consistent with previous observations the shock rate per hour fluctuated over a range of ± 10 shocks. Examination of cumulative records in Figure 15 reveals the individual differences in baseline response and shock rates between the three subjects, on R*S 80 sec. Performance of the three animals remaining on the R*S 20 sec. parameter is shown in Figure 16 (See also Table 2, in appendices). Stable rate differences engendered by the R*S 20 sec. and R*S 80 sec. parameters respectively persisted throughout the experiment.

(ii) Findings emerging from the first series of drug determinations.

In the Method (Procedure section) it was pointed

Figure 13

Representative cumulative records showing the effects of increasing the number of responses required to avoid shock from 1 to 5 on R*S 20 S*S 5 parameters. First 40 minutes of each record are shown. Oblique pips denote shocks. Note the 'bursts' of shocks occurring during 'warm-up' at the beginning of each session. Rat HF8.

fig.13

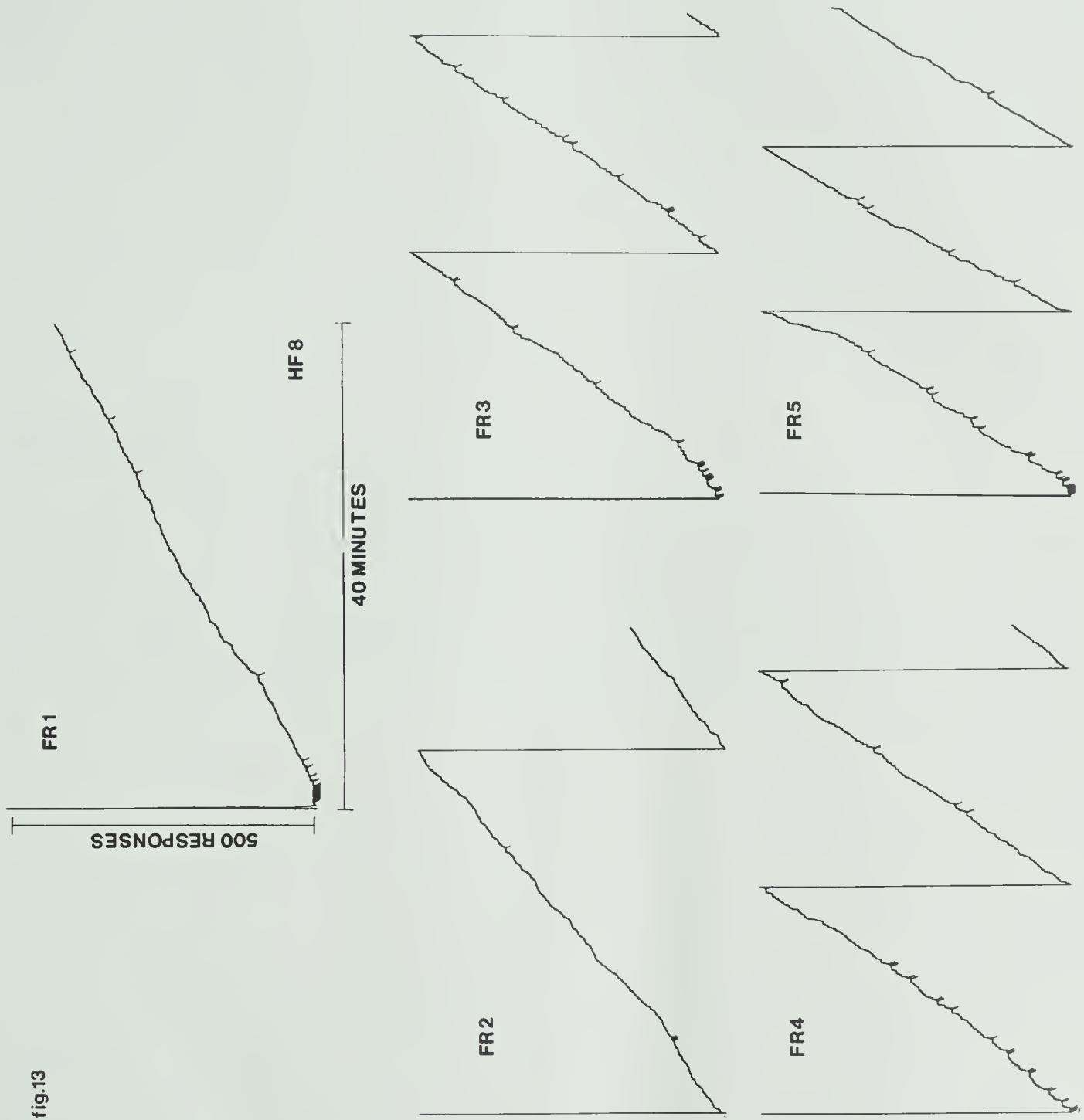


Figure 14

R*S interval parameter manipulation, R*S 20 sec. to R*S 80 sec. Overall response rate per minute (solid line) and average shock rate per hour (dotted line) for 16 consecutive sessions. Rat HF8.

fig.14

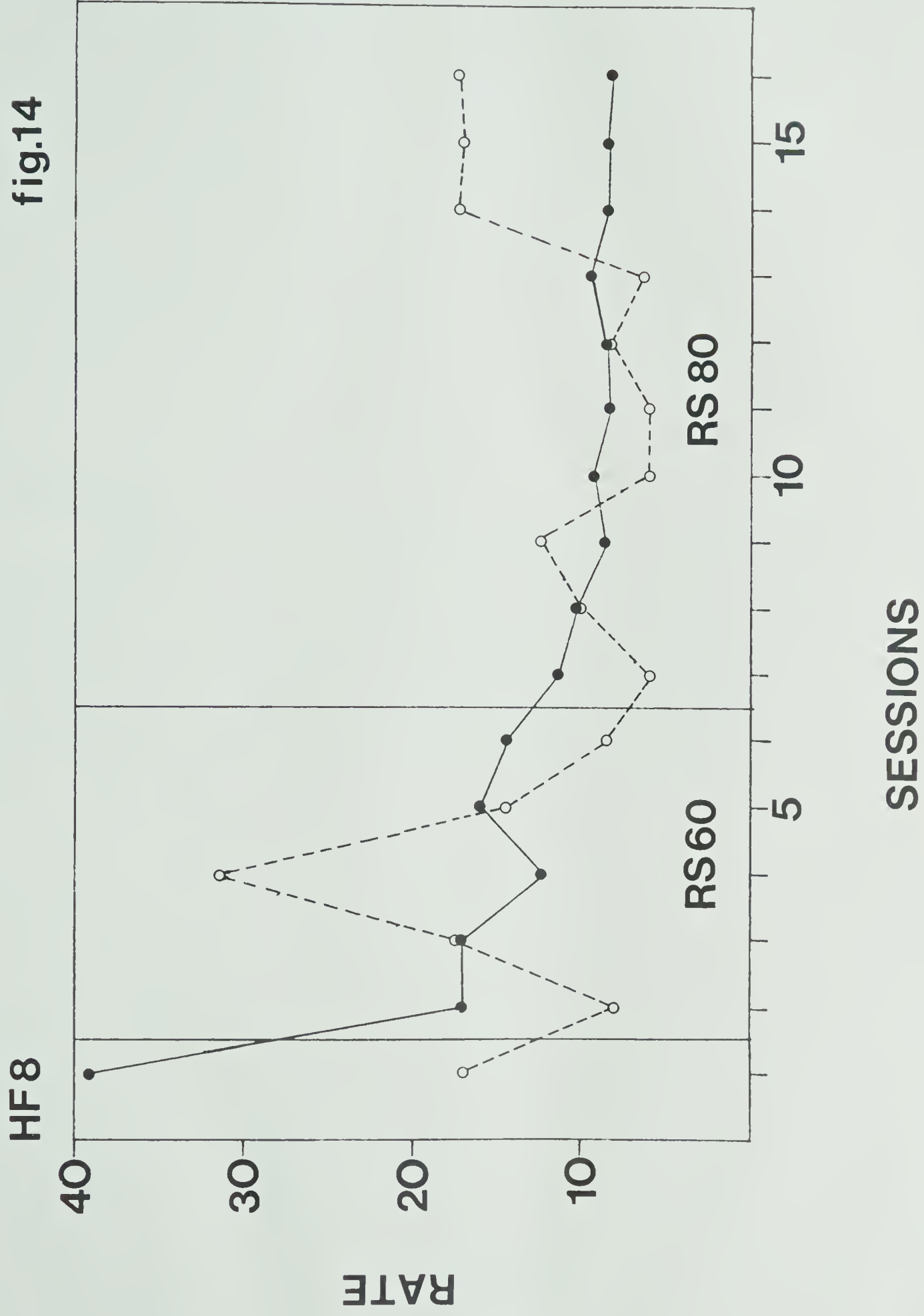


Figure 15

Representative cumulative records of results on R*S 80 S*S 5 FR 5 parameters. Records show first 2 hours of the experimental session. Inter-subject variability in baseline response and shock rates is prominent. Oblique pips denote shocks. Rats HF4, HF3 and HF8.

R★S80 S★S5 FR5

HF4

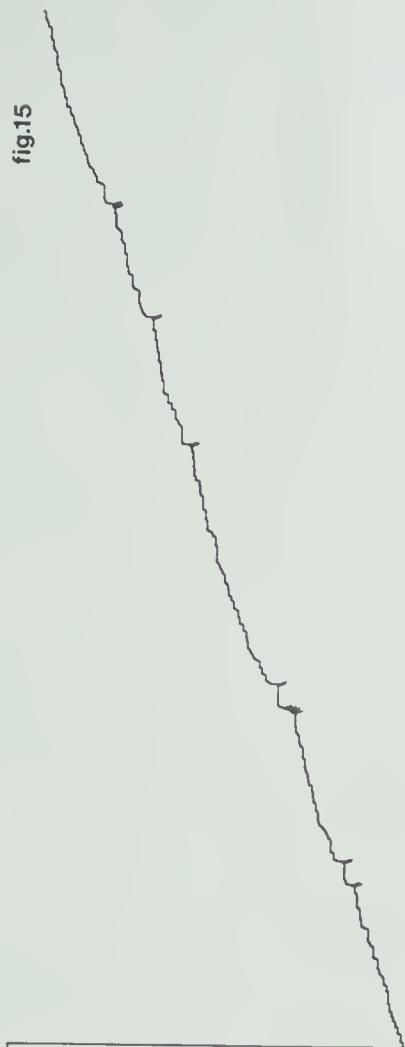
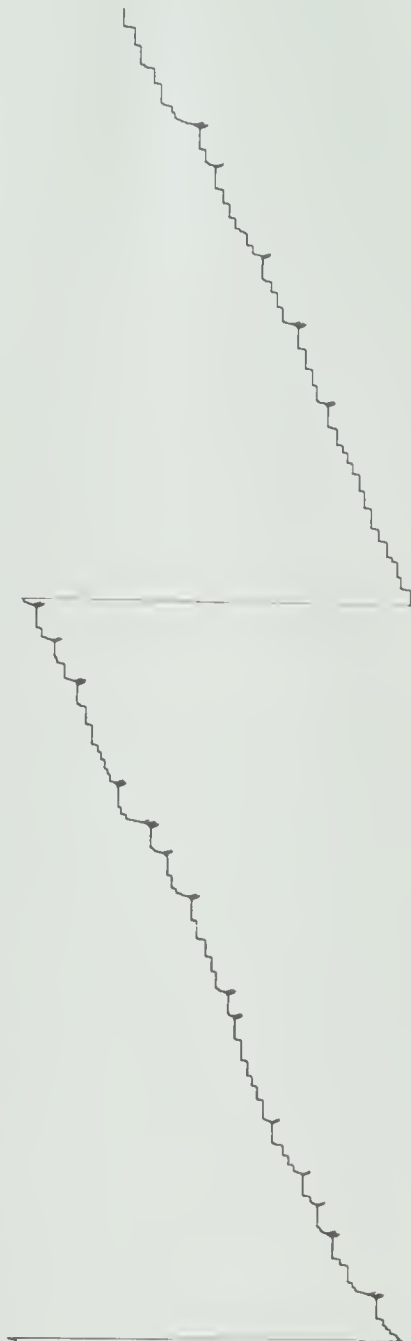


fig.15

500 RESPONSES

HF3



40 MINUTES

HF8

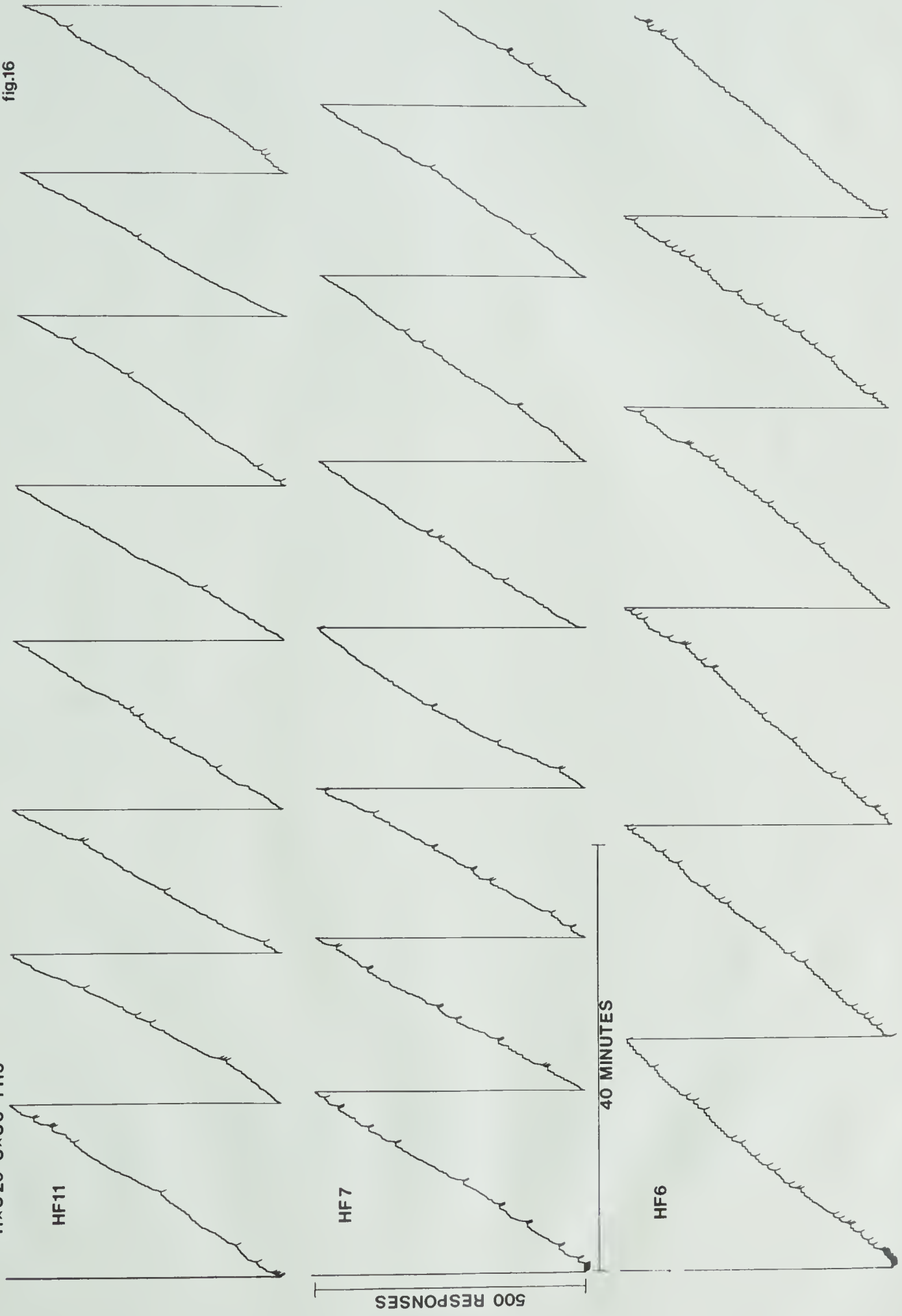


Figure 16

Representative cumulative records of results on R*S 20 S*S 5 FR 5 parameters. Record shows first 2 hours of the experimental session. Individual differences in response and shock rates are evident. Oblique pips denote shocks. Rats HF11, HF7 and HF6.

R★S20 S★S5 FR5

fig.16



out that the drug (or saline solution) was administered one minute prior to the beginning of the experimental session. The time-course of drug action was observed to be maximally effective during the first 40 minute period, decreasing thereafter, to near control rates by the third 40 minute period, depending upon the dosage given. The results then, during this phase of the experiment, will be reported in terms of the first, second and third, 40 min. periods comprising the experimental session.

At the outset of this phase of results some general comments are appropriate: First, in the present state of knowledge of drug-behavior interactions, using aversive stimuli, the results of the administration of graded dosages of a psychoactive agent cannot be interpreted solely in terms of a drug-response rate effect. Effects of the drug on ongoing behavior must be examined in terms of the parameters controlling the behavior and the response and shock frequencies engendered by the schedule parameters in the individual subjects. Second, the results of one R*S 80 animal (HF9) have been omitted since the animal died during the third 16 mg/kg determination, thus not completing the remainder of the determinations at the 4 and 8 mg/kg dose levels.

The general trend, in all animals under each dose of methylphenidate, was an increase in response rate over that observed under control conditions. The results for each dosage are now described in greater detail.

Figure 17 represents the results of four determinations of 4 mg/kg methylphenidate (See also Table 3, in appendices). All subjects show an increase in response rate over control conditions. Rats HF6 and HF3 show a relatively small increase in rate accompanied by a sizeable and variable shock frequency increase. Those subjects, on the other hand, who display a lower shock frequency under control conditions, produce higher overall response rates under drug conditions.

Examination of the cumulative record in Figure 18 shows the time-course of drug action and the temporal distribution of responses and shocks. Subjects HF7, HF8 and HF3 show increased incidence of escape behavior following the administration of the drug. This is evident in the increased shock frequency occurring during the first 5 to 15 minutes of the session. Drug-induced rate increases for HF3 became evident only after approximately one half hour from the beginning of the session. Rat HF11, on the other hand, showed consistent drug-induced rate increases and few shocks for all determinations administered.

Figure 17

Overall response rate per minute (solid bars) and average shocks per 40 minute period (indented bars) for four determinations of methylphenidate at the 4 mg/kg dose level. Vertical lines represent the range, and C shows control rates. Rats HF11, HF7, HF6, HF3 and HF8.

RESPONSE AND SHOCK RATES

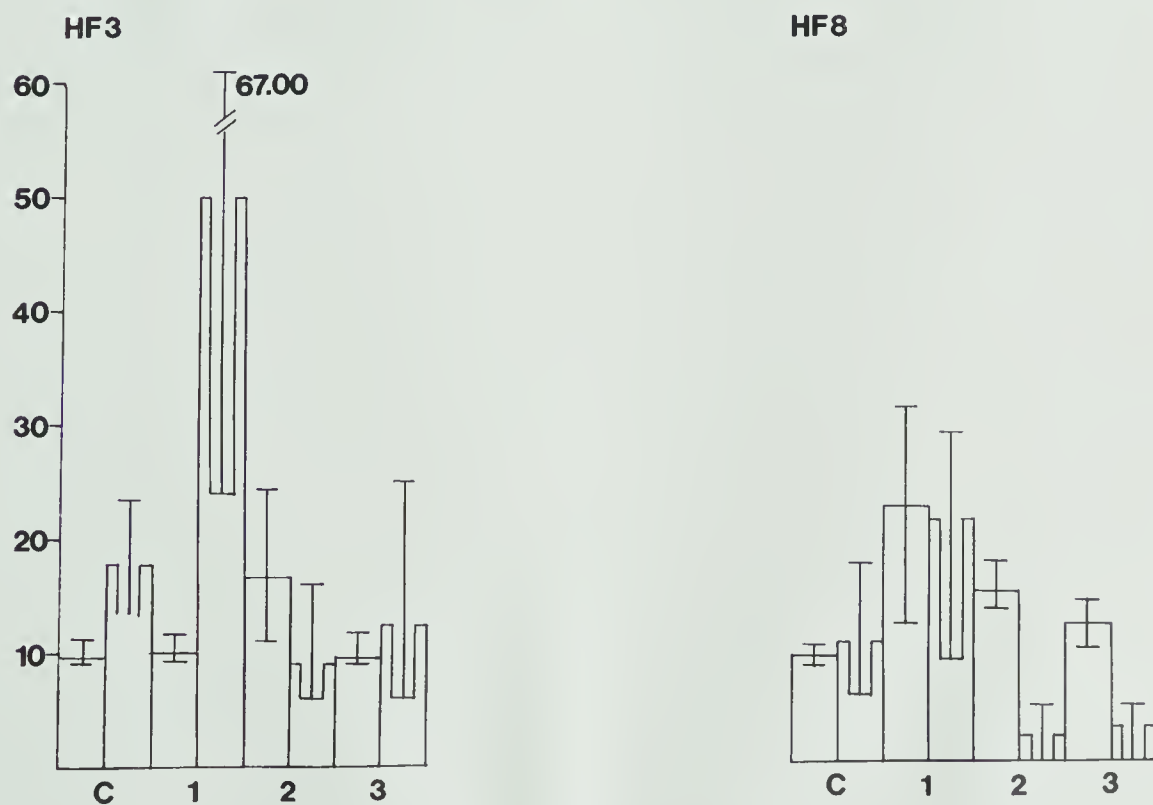
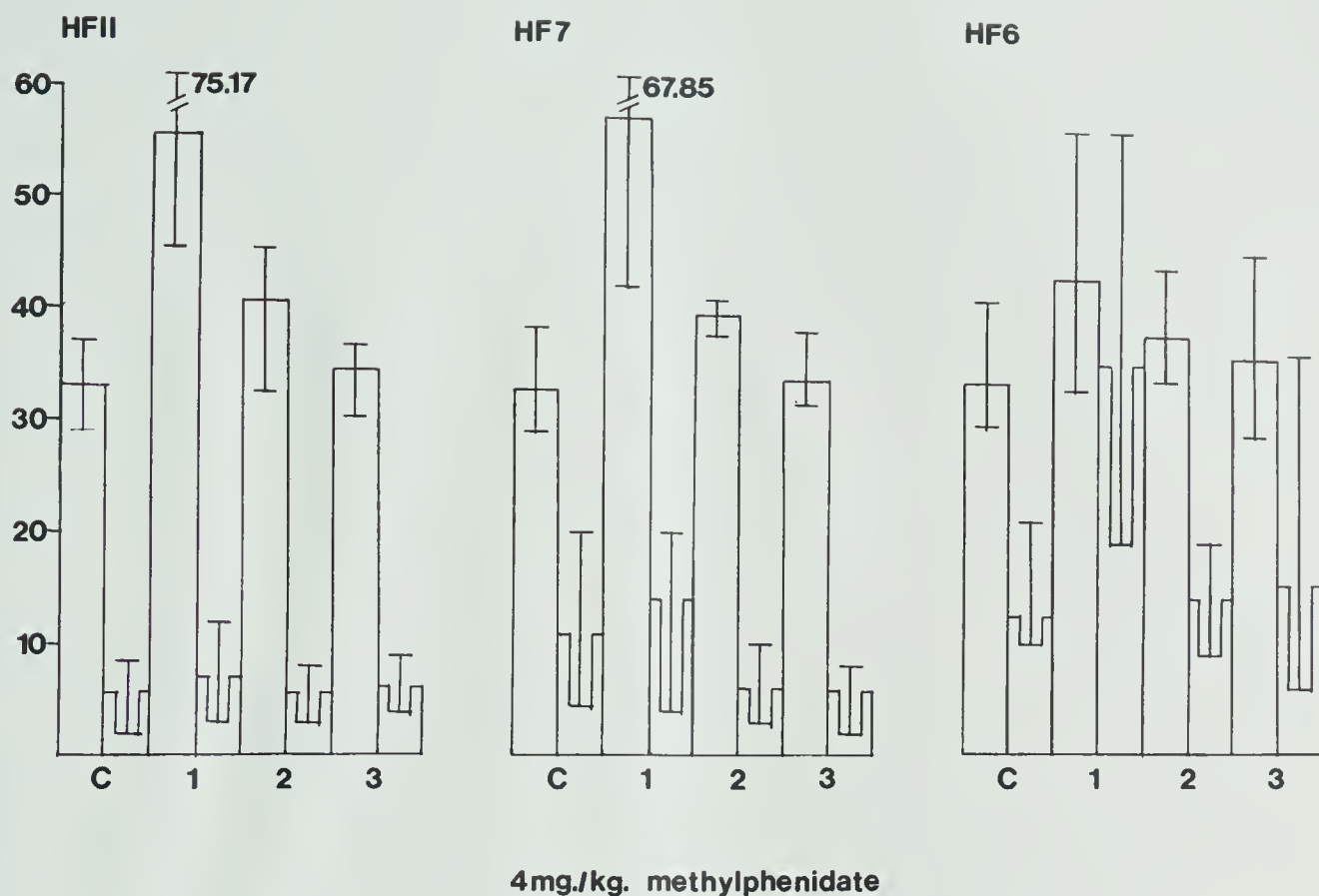


fig.17

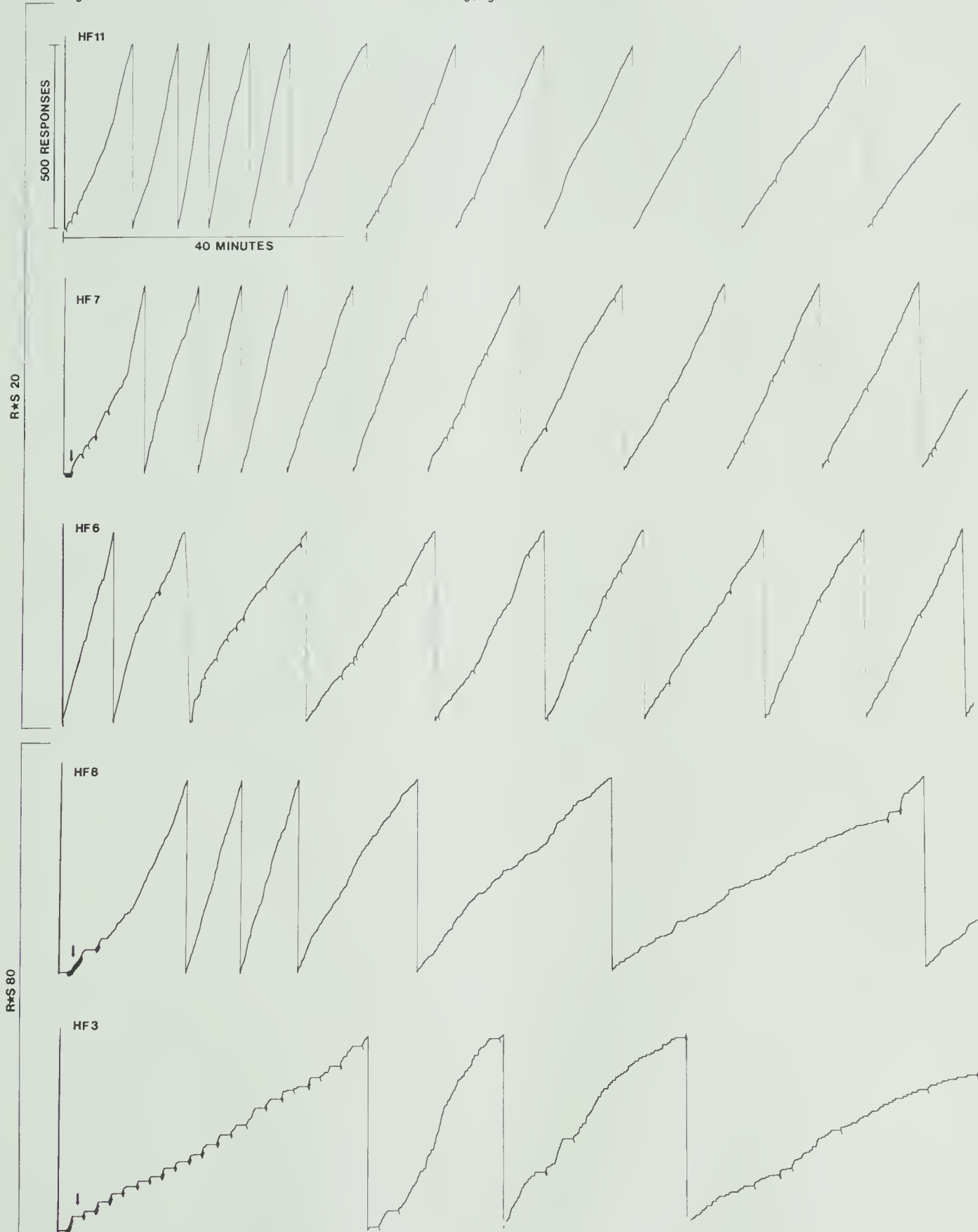
40 MINUTE PERIODS

Figure 18

Representative cumulative records showing results of methylphenidate at the 4 mg/kg dose level. Oblique pips denote shocks. Arrows show beginning-of-session escape responding. Records represent the first 2 hours of the experimental session. Rats HF11, HF7, HF6, HF8 and HF3.

fig.18

4mg./kg.



Results of administration of 8 mg/kg methylphenidate are shown in Figure 19. (See also Table 4, in appendices). Consistent with the observations of the 4 mg/kg dose level is that all subjects show an increase in response rates over control conditions. However, the increases are generally larger at the 8 mg/kg dose level. Larger over-all response rate increases are observed in the R*S 20 sec. animals whose baseline response rates, under control conditions, are in the order of three times those engendered by the R*S 80 sec. parameter.

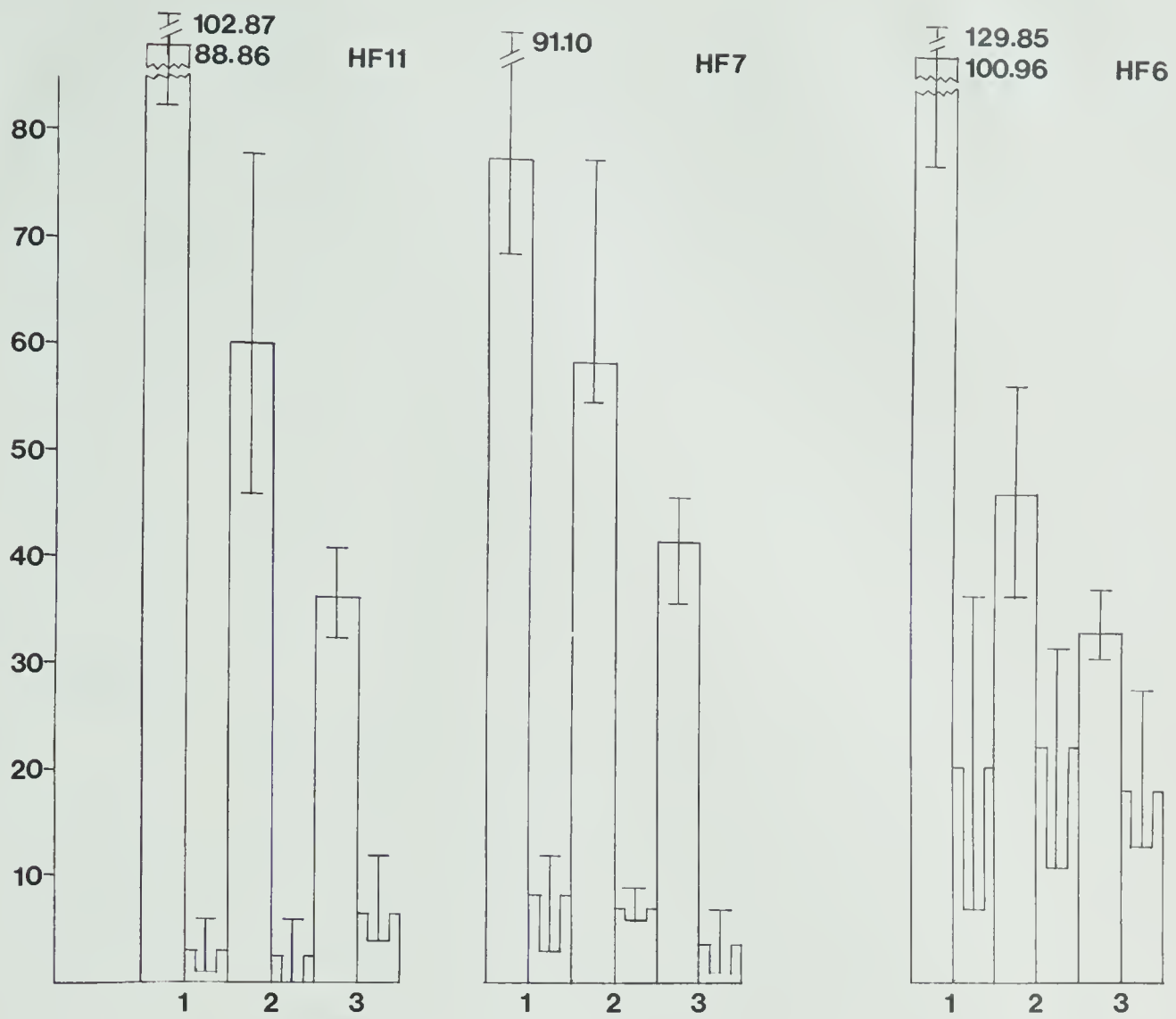
Figure 20 shows representative cumulative records for the 8 mg/kg dose administrations. As would be expected, the 8 mg/kg dose shows a more pronounced time-course effect, (than the 4 mg/kg dose) lasting up to the third 40 min. period of the session. Animals HF6, HF8 and HF3 again show post-shock bursting at the beginning of the first period. This is particularly evident in HF3 and consistent with observations from the 4 mg/kg determinations. Those subjects receiving few shocks under control conditions (HF11 and HF8), had a smaller range, in RPM at the 8 mg/kg dose than those animals who receive many shocks under control conditions (HF7, HF6 and HF3).

Response rate increases with the 16 mg/kg determinations were similar to those produced by the 8 mg/kg dose level, but persisted longer (up to the fourth 40 min period).

Figure 19

Overall response rate per minute (solid bars) and average shocks per 40 minute period (indented bars) for four determinations of methylphenidate at the 8 mg/kg dose level. Vertical lines represent the range. Rats HF11, HF7, HF6, HF3 and HF8.

RESPONSE AND SHOCK RATES



8mg./kg. methylphenidate

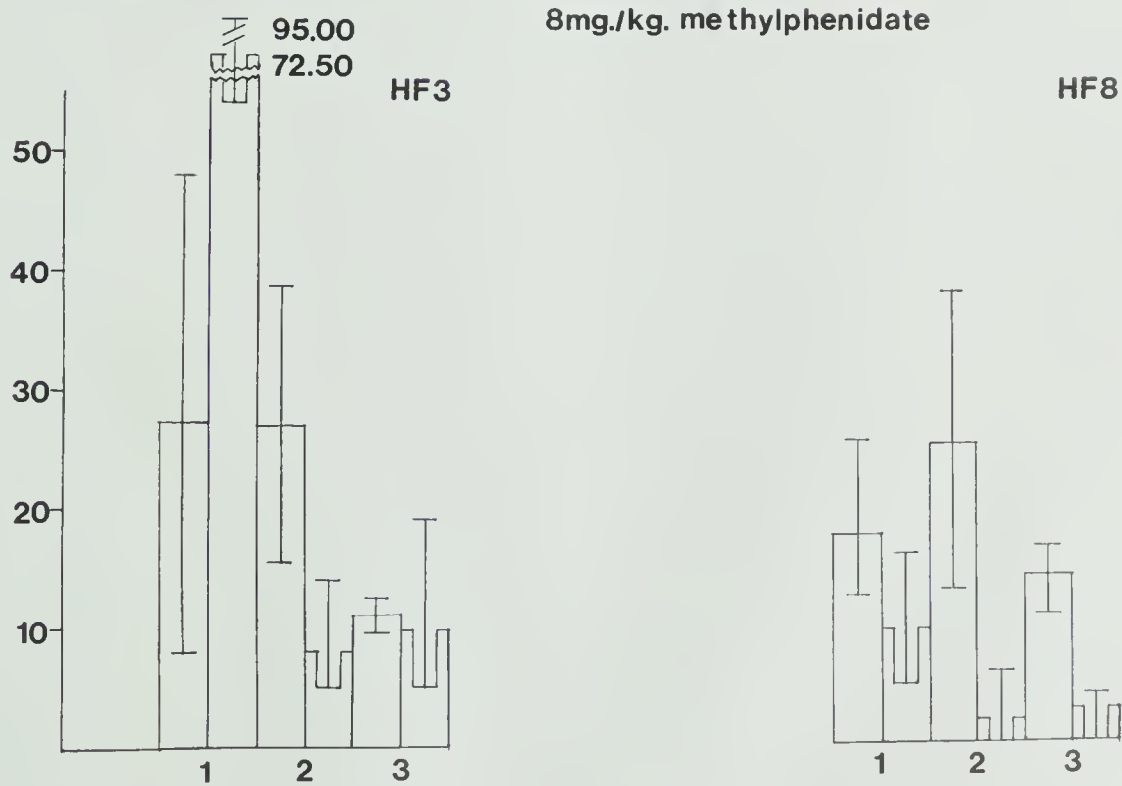


fig.19

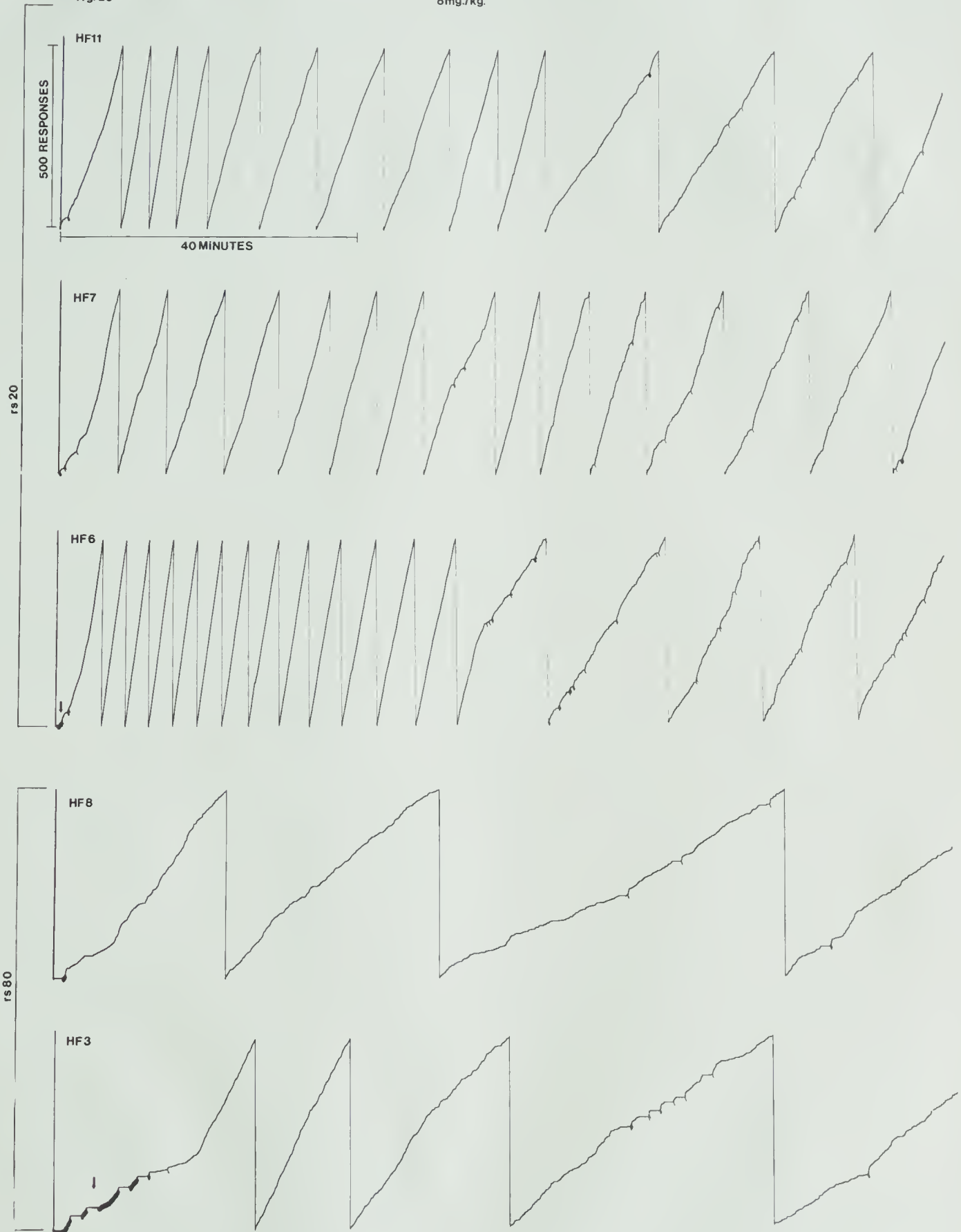
40 MINUTE PERIODS

Figure 20

Representative cumulative records showing results of methylphenidate at the 8 mg/kg dose level. Oblique pips denote shocks. Arrows show beginning-of-session escape responding. Records represent the first 2 hours of the experimental session. Rats HF11, HF7, HF6, HF8 and HF3.

fig. 20

8mg/kg.



Results are shown in the histograms of Figure 21 and in the representative cumulative records in Figure 22. (See also Table 5, in appendices). At this highest dose level, those animals displaying post-shock bursting during the first 40 minute period encountered some difficulty. HF6 received a high incidence of shocks prior to rate increases induced by the drug. HF3 displayed similar behavior initially, then, early in the third period, collapsed in an apparent state of exhaustion. The 16 mg/kg determinations were then discontinued for these animals. (A second R*S 80 sec. animal, mentioned earlier, whose data is not being presented, could not effectively eliminate shocks during the first period of the third 16 mg/kg determinations, and then died in the experimental chamber).

Both the 8 mg and 16 mg/kg dose level results emphasize the variability of drug-rate effects with differences in 'warm-up' between subjects. Rat HF11 (Figure 21) with little 'warm-up' effects displayed consistent rate increases within a narrow range over four determinations. Rat HF6 (Figure 21), on the other hand encountered a relatively high shock frequency initially, which varied over a large range; the rate increases associated with this period are variable over a wide range for four determinations.

Central to the aims of the study is the observation that overall drug-induced rate changes alone, showing the

Figure 21

Overall response rate per minute (solid bars) and average shocks per 40 minute period (indented bars) for four determinations of methylphenidate at the 16 mg/kg dose level. Vertical lines represent the range. Rats HF11, HF7, HF6, HF3 and HF8.

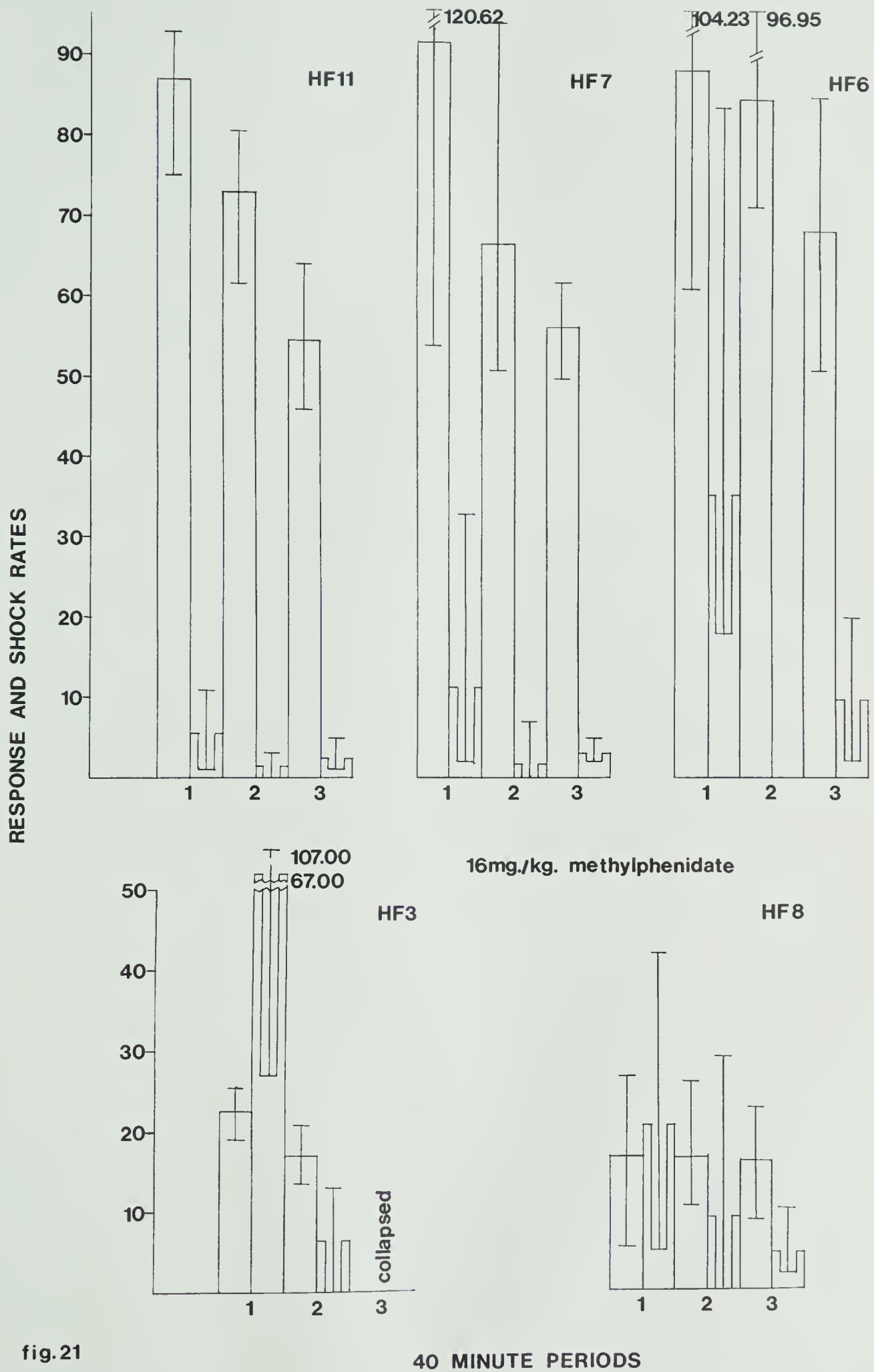


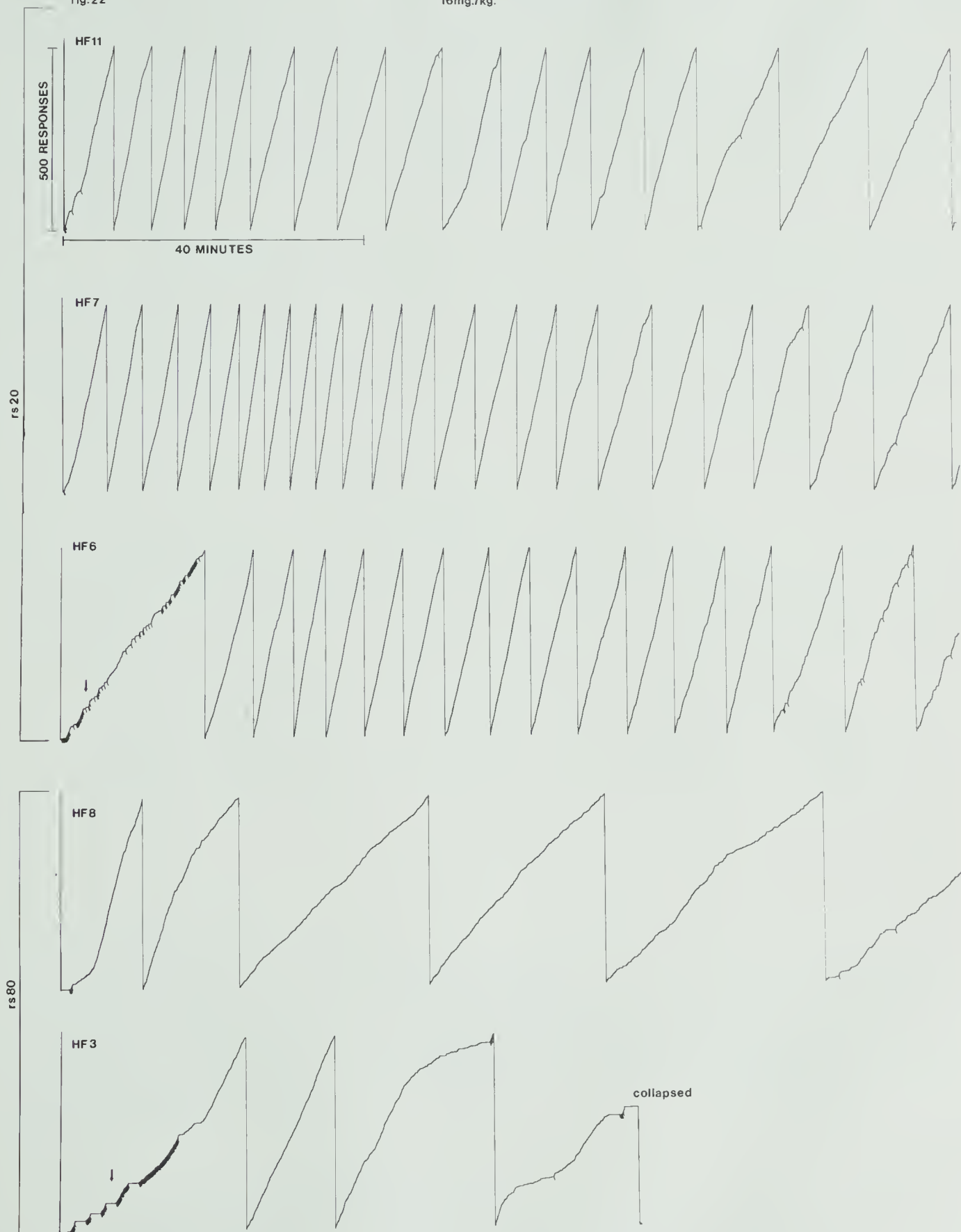
fig.21

Figure 22

Representative cumulative records showing results of methylphenidate at the 16 mg/kg dose level. Note the increased incidence of beginning-of-session escape responding in HF6 and HF3. Oblique pips denote shocks. Records represent the first 2 hours of the experimental session. Rats HF11, HF7, HF6, HF8 and HF3.

fig. 22

16mg./kg.



absolute increments in responding, do not completely express the results. Results engendered by the three graded doses must also be considered in terms of the relative behavioral output of the individual subjects in that twice as many drug-induced responses should mean twice as much behavior.¹

Table I represents the relative ratio of increases in behavioral output² over control rates in the individual subjects resulting from the first series of drug tests.

TABLE I

Subjects	4 mg/kg	8 mg/kg	16 mg/kg
HF 11 R*S 20	1.70	2.70	2.64
HF 7 R*S 20	1.73	2.36	2.79
HF 6 R*S 20	1.30	3.03	2.64
HF 8 R*S 80	2.30	2.00	1.89
HF 3 R*S 80	1.00	2.70	2.20

¹ Honig (1966) has suggested that: "... it is meaningful to talk about the amount of responding; twice as many responses mean twice as much behavior, while it is less certain that twice the amplitude, half the latency, etc., of a response have the same kind of direct numerical implication". (p.6).

² Values were determined by:

$$\frac{\text{Drug Rate}}{\text{Control Rate}} = \text{ratio of increase in behavioral output.}$$

It is apparent from Table I that, although the R*S 20 sec. subjects show greater absolute increases in response rate than the R*S 80 sec. subjects, relative increases in behavioral output are very similar for all subjects regardless of their respective schedule parameters.

Results of sessions preceeded by injections of isotonic saline are shown in Figure 23 and in representative cumulative records in Figure 24. (See also Table 6, in appendices). These results can be compared with the previous data representing the 4,8 and 16 mg/kg doses of methylphenidate. No discernible effects of saline injections were noted; response and shock rates were consistent with the results obtained under control conditions without injections.

A central point arising from this first series of drug determinations concerns the variability of drug effects associated with the differences in 'warm-up' at the outset of the session. Those subjects displaying persistent shock-elicited responding (eg HF6 and HF3) under control conditions, displayed greater variability in rate increase at each dose. Inter-subject differences in maximal rate increases at the three dosages are evident. Subject HF7 showed a monotonic increase in rate as a function of increasing dosage, while HF8, on the other hand, showed a monotonic decrease in rate as a function of increasing dosage. Subjects HF11, HF6 and HF3 showed maximal rate increases at the 8 mg/kg dosage level.

Figure 23

Overall response rate per minute (solid bars) and average shock rate per 40 minute period (indented bars) under isotonic saline conditions. C represents control rates. Vertical lines represent the range. Rats HF11, HF7, HF6, HF3 and HF8.

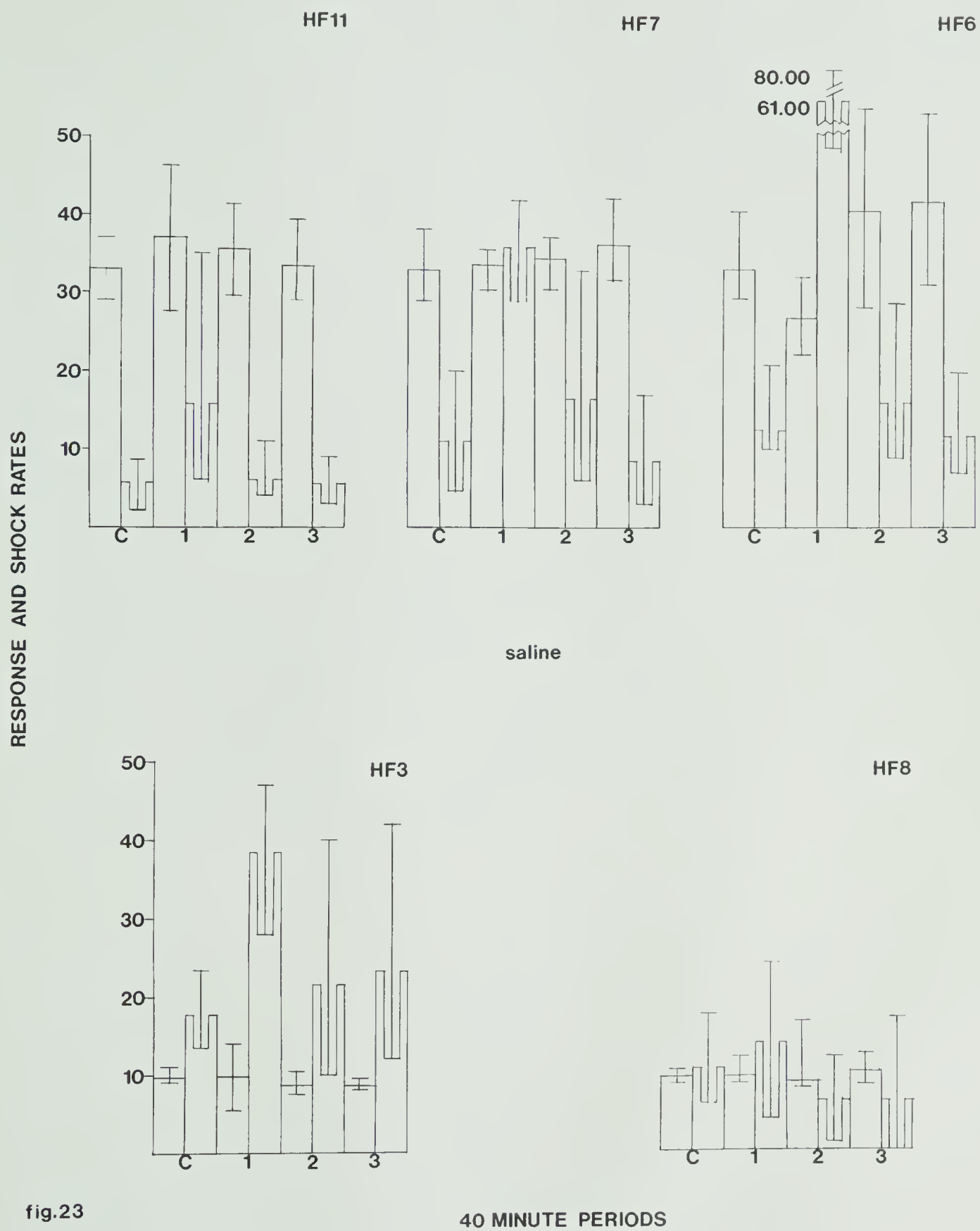
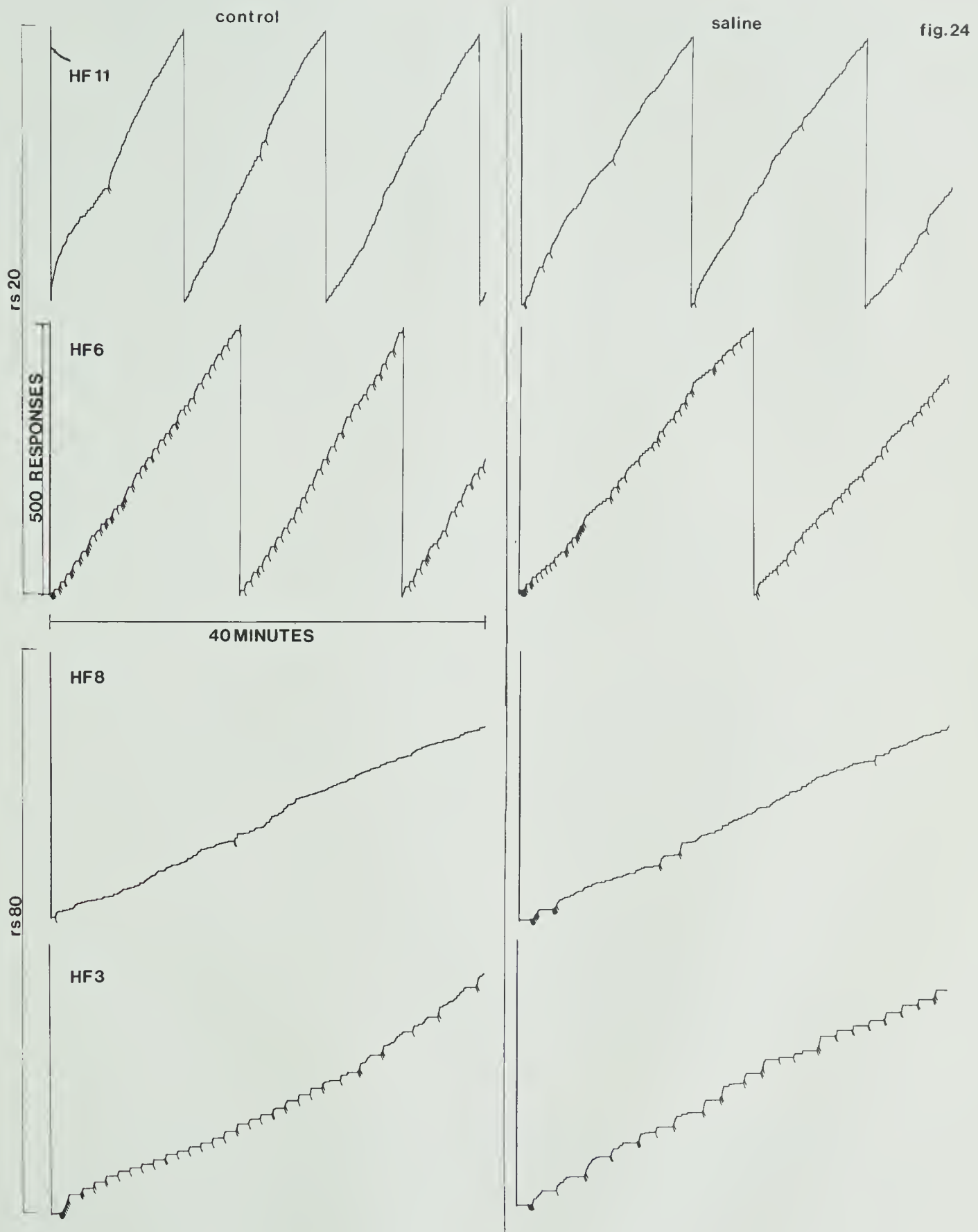


Figure 24

Representative cumulative records showing control and saline response and shock rates. Individual differences between subjects is very evident. Note the high shock frequency of HF6 and HF3. Oblique pips on records denote shocks. Rats HF11, HF6, HF8 and HF3.



(iii) Paired fixed ratio/variable interval
restabilization

This phase, and the phase following, mark procedural changes in the experiment. With the possibility that the 'warm-up' and drug effects had been confounded in the first series of drug determinations, as previously reported, it was necessary to restabilize behavior and repeat the series of determinations with the procedural modifications outlined in the Method section.

It will be recalled that the modification of the experiment led to two important changes:

- 1) The drug injections were not given until two 40 minute periods of control ratio avoidance had occurred.
- 2) The variable interval period of shock presentation afforded a period in which each pair of animals (one, R*S 20 sec; the other R*S 80 sec.) received an identical frequency and temporal distribution of shocks, irrespective of differences in response rate between the pair.

Changes in subjects also occurred during this phase (as previously stated in the Procedure). Rat HF9

that had died during the first series of drug determinations was replaced by HF4. Animals HF6 and HF3 were too unstable and since they encountered some difficulties under drug conditions, were deemed unreliable and dropped from the experiment. The pairs of subjects became: HF11 (R*S 20) with HF8 (R*S 80) and HF7 (R*S 20) with HF4 (R*S 80). HF11 and HF8 completed the experiment under fixed ratio/variable interval conditions and HF7 and HF4 completed the experiment under variable ratio/variable interval conditions. Since the variable interval was operative during the third 40 minute period, the results for the remainder of the experiment will be reported in terms of the second, third and fourth 40 minute periods of the experimental session.

Results of the fixed ratio/variable interval re-stabilization are presented in Figure 25. Representative cumulative records of HF11 and HF8 are shown in Figure 26 (See also Table 7, in appendices). The main result in this phase is that it was found possible to maintain baseline avoidance response rates, consistent with those found under fixed ratio avoidance, by means of a variable interval four minute (V.I.4') presentation of unavoidable shocks. To our knowledge this is the first time that this has been successfully demon-

Figure 25

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) under FR 5/VI 4 min. control conditions. (Black indented bars represent variable interval 4 min. shock presentation). Vertical lines represent the range. Rats HF11 and HF8.

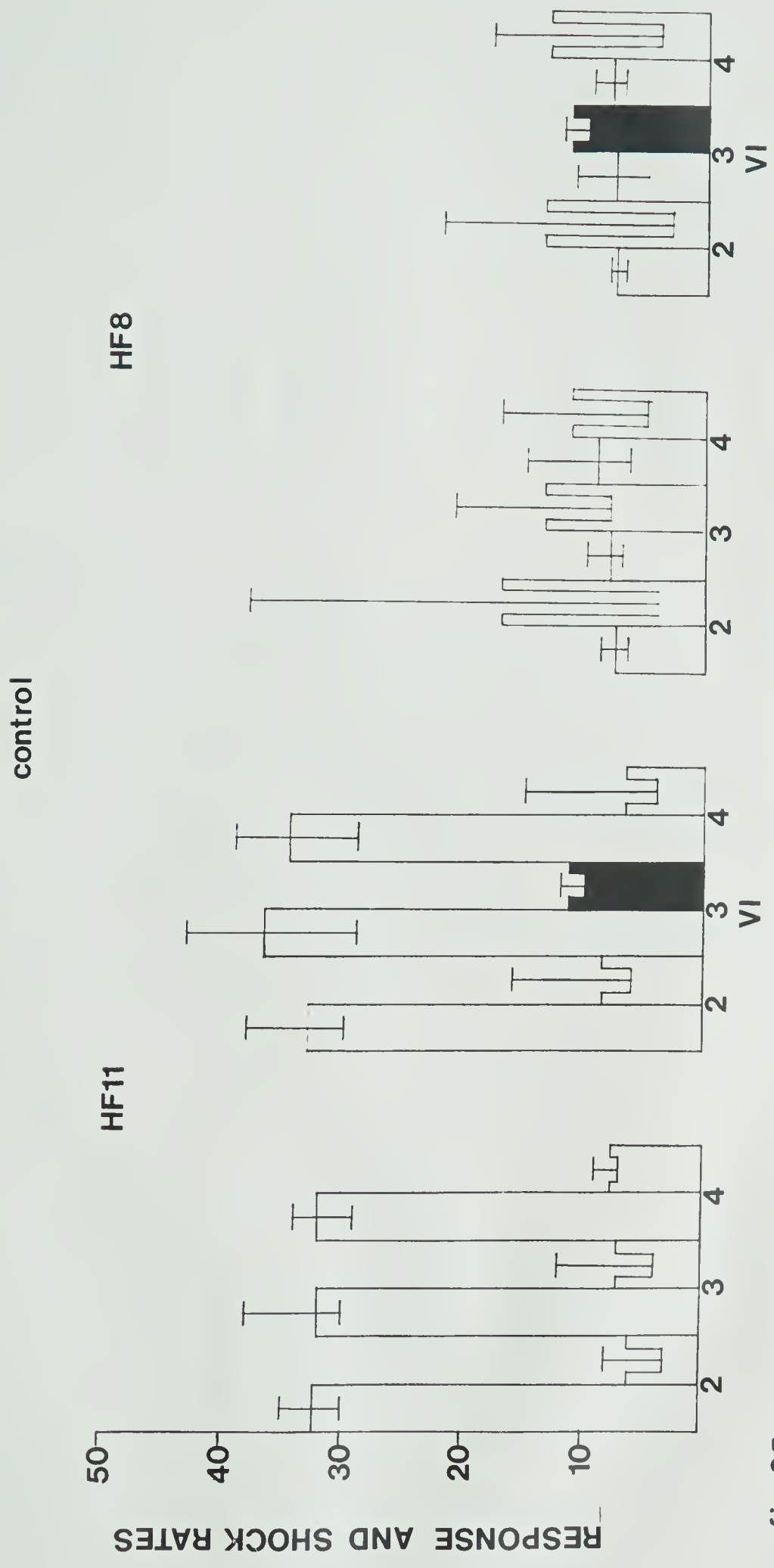


fig.25

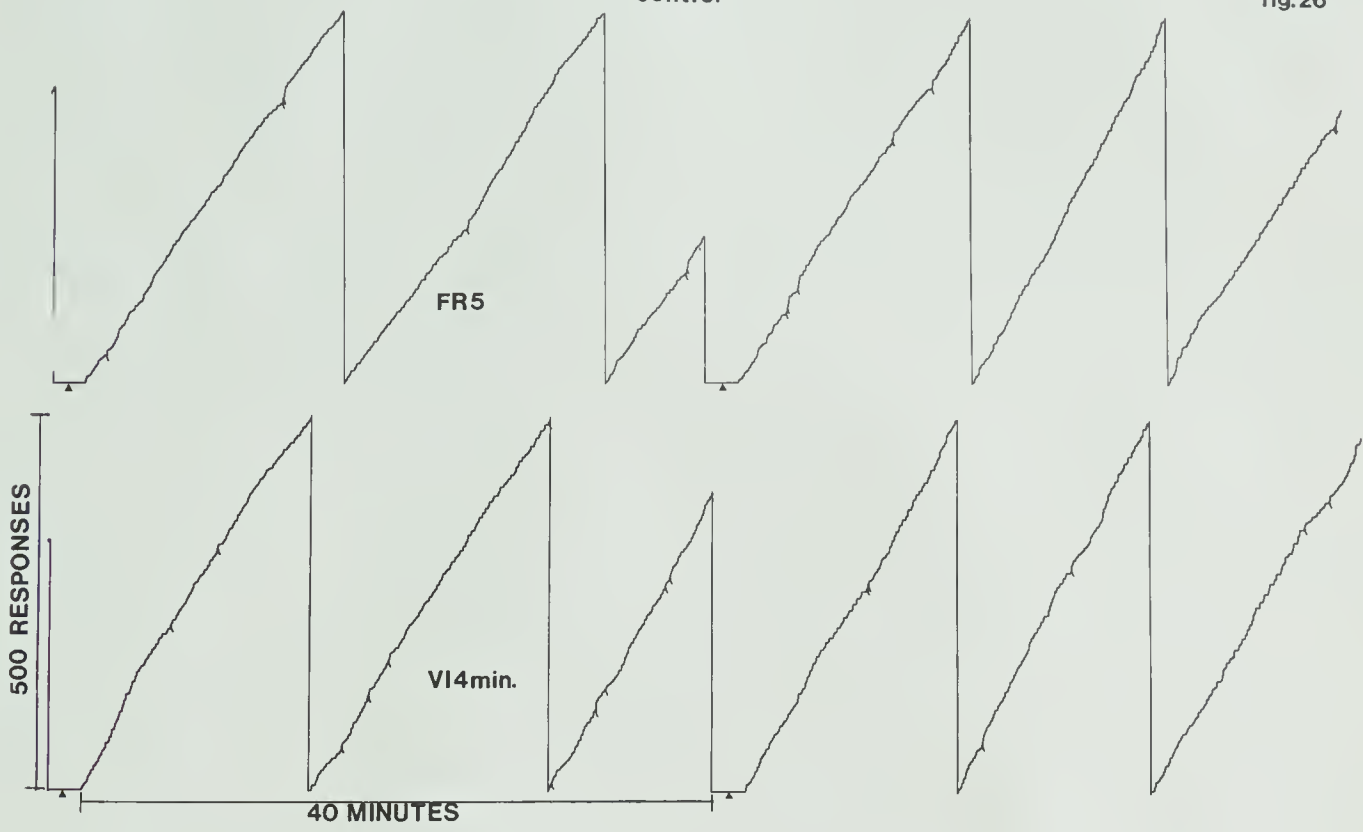
Figure 26

Cumulative records showing FR 5 and VI 4 min. control baselines. Records represent the 3rd and 4th forty minute periods of the session. Black triangles show 2 min. time-out periods between 40 minute running periods. Note the similarity in rates between FR and VI periods. Oblique pips on records denote shocks. Rats HF11 and HF8.

HF11 rs 20

control

fig.26



HF8 rs 80

FR5

VI4min.



strated over a prolonged period of time. Overall response rates under the variable interval condition were very similar to fixed ratio control rates in both subjects, although a greater degree of variability was observed under the V.I. as compared to fixed ratio conditions. Consistent with previous observations, HF8 displayed persistent post-shock bursts of responding through the first period. An equally interesting observation with HF8 is the different patterns of shock maintaining the avoidance behavior. Examining the cumulative record of this subject (Figure 26), one can see that, under fixed ratio conditions, shocks rarely occur singly but rather in bursts of two, three or more. However, during the variable interval period, shocks rarely occur in bursts, and are usually aperiodic, yet maintain the same rate of responding as under the fixed ratio conditions.

A comment on the two minute time out between the successive 40 minute periods is appropriate here. Prior to beginning the restabilization sessions a matter of concern was whether or not a 'warm-up' effect would be observed at the beginning of each 40 minute period that had been preceded by the two minute time-out. Visual inspection of the cumulative records (Figure 26) reveals that 'warm-up' effects, for both subjects, occur only at

the start of the experimental sessions. The remaining periods of the session preceeded by the two minute time-out did not display characteristic 'warm-up' effects. This is a particularly important observation with respect to the administration of the drug in the second series of determinations immediately following.

(iv) Findings emerging from the second series of drug determinations

Restabilization for both animals, HF11 (R*S 20") and HF8 (R*S 80") was completed successfully within ten sessions each of fixed ratio and variable interval conditions. In the second series of determinations, to be reported below, reference will be made, for comparison, to the preceeding series of determinations for the same subjects.

Consistent with the results emerging from the first series of drug determination is the overall observation of increased response rates in both subjects over their respective baseline control conditions.

Figures 27, 28 and 29 show the results of four determinations each of 4, 8 and 12 mg/kg under fixed ratio and variable interval conditions. (See also Tables 8, 9 and 10, in appendices). Representative cumulative records of the performances of HF11 and HF8 are shown in Figures 30, 31 and 32.

Figure 27

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) for four determinations of methylphenidate at the 4 mg/kg dose level. (Black indented bars represent variable interval 4 min. shock presentation). Vertical lines represent the range. Rats HF11 and HF8.

4 mg./kg

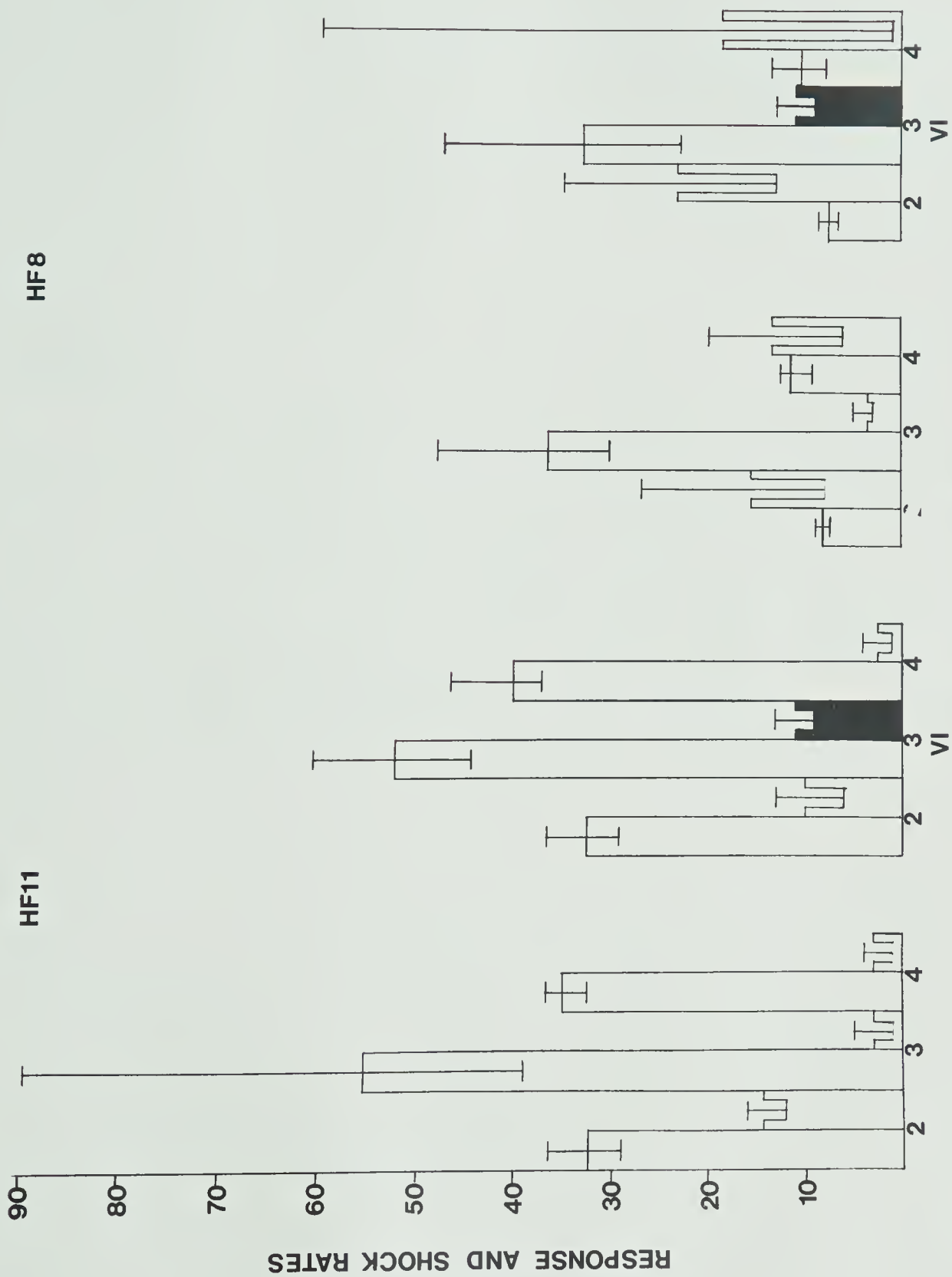


Figure 28

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) for four determinations of methylphenidate at the 8 mg/kg dose level. (Black indented bars represent variable interval 4 min. shock presentation). Vertical lines represent the range. Rats HF11 and HF8.

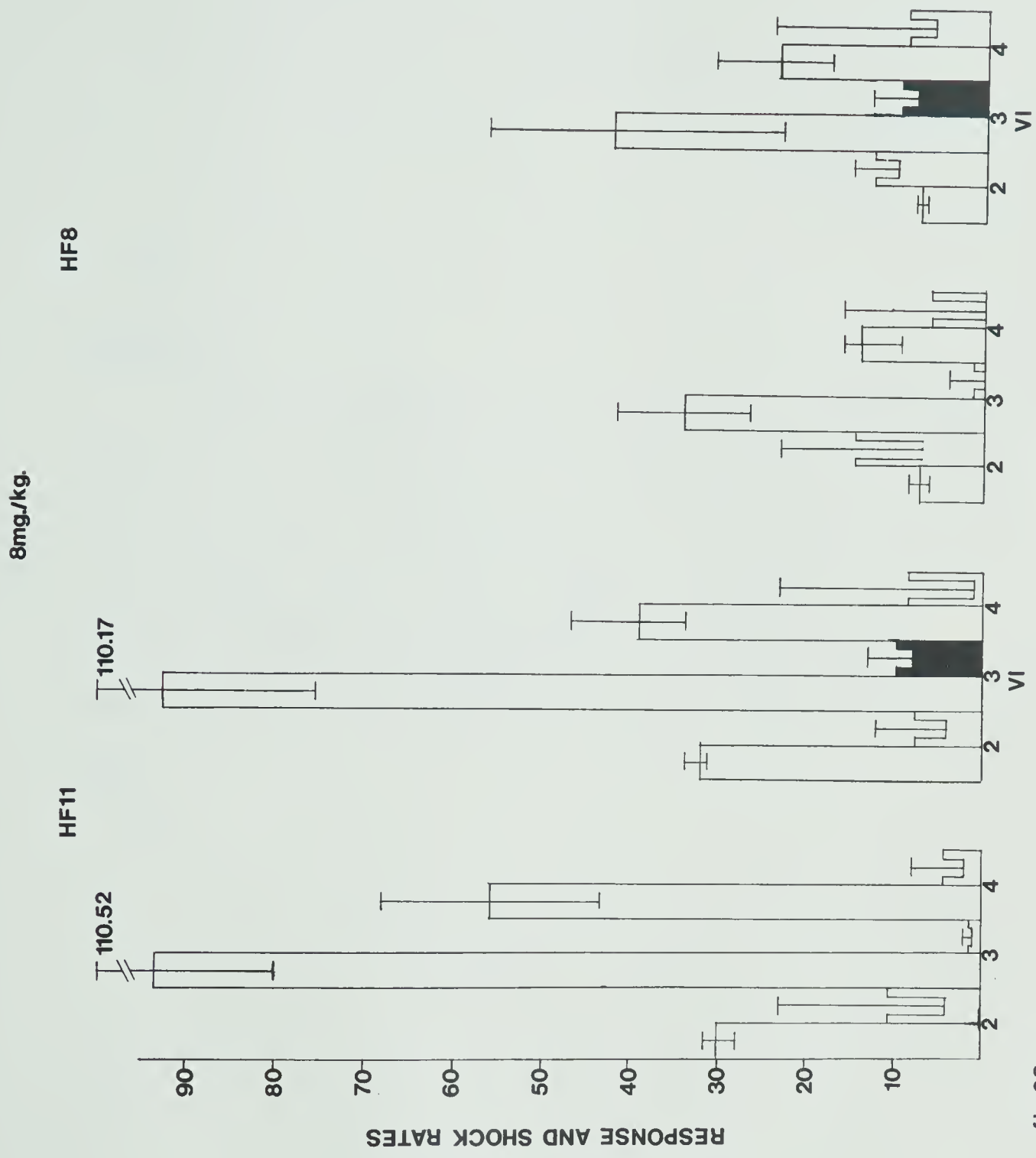


fig.28

Figure 29

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) for four determinations of methylphenidate at the 12 mg/kg dose level. (Black indented bars represent variable interval 4 min. shock presentation). Vertical lines represent the range. Rats HF11 and HF8.

12mg./kg.

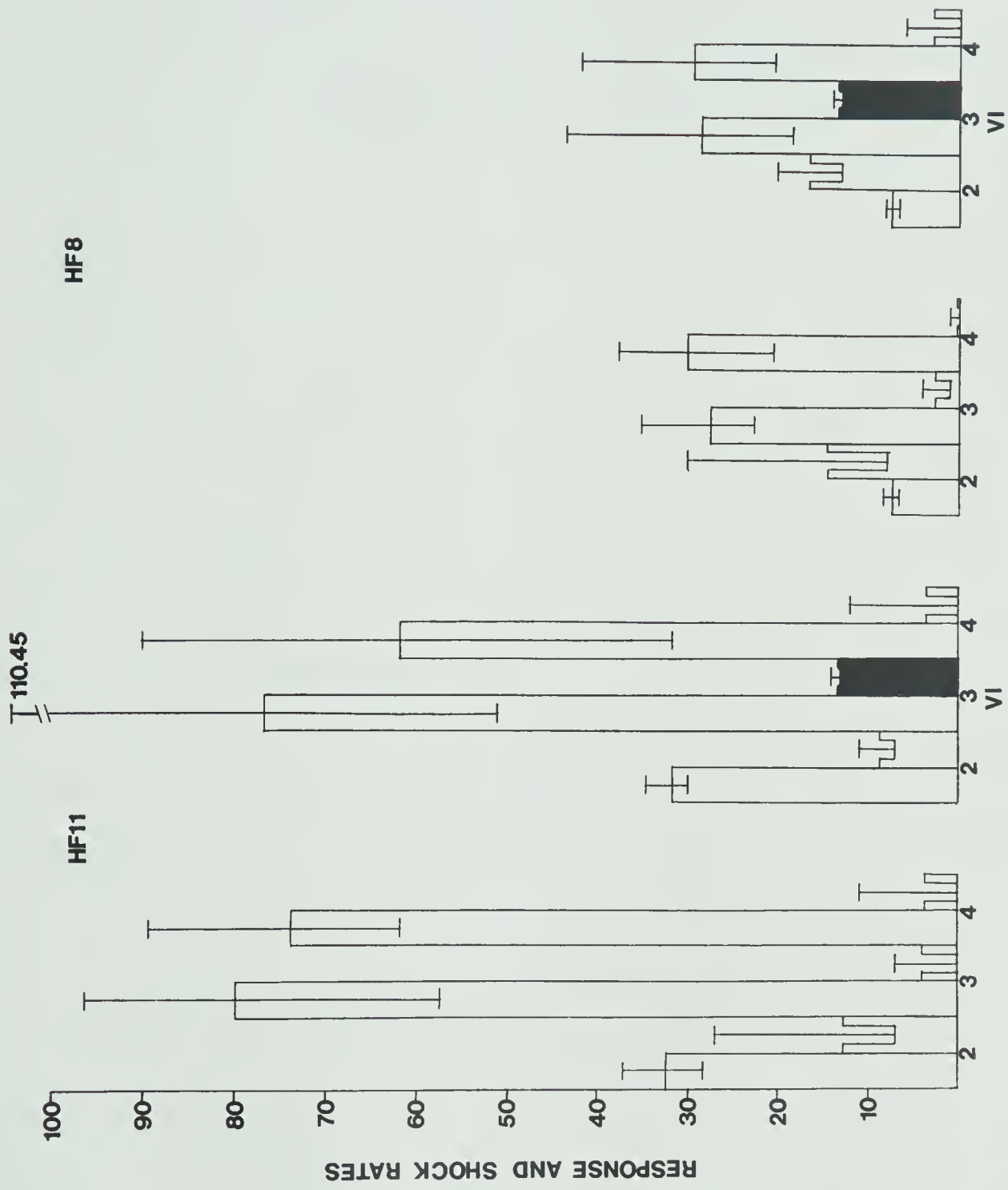


fig. 29

Overall rate increases at the 4 mg/kg dose level in HF11 under fixed ratio conditions are very similar to those found in the first series but have a greater range over four determinations. Variable interval results were consistent with respect to overall rate increases, however, the range was considerably smaller for the four determinations administered.

Rat HF8, as compared to HF11, displayed an overall higher rate of responding than in the first series with the 4 mg/kg dosage throughout the second series, under both fixed ratio and variable interval conditions. Under fixed ratio conditions HF8 shows a slightly reduced range, while under variable interval conditions the range, for four determinations is increased. This is just the reverse of that observed for HF11.

Results of the 8 mg/kg determinations differ for HF11 and HF8. At this dosage HF11 shows the largest increments in overall response rates under both the fixed ratio and variable interval conditions. These rates are slightly increased over those observed in the first series. Rat HF8, however, shows the largest increments in response rate under the variable interval condition only. Under fixed ratio conditions the overall response rate was decreased from that observed at the 4 mg/kg dose level. The average shocks and the range

of shocks per 40 minute period, under the 8 mg/kg drug conditions, are considerably less in the second series for HF8. Overall drug-rate increases for both subjects, persisted into the fourth period of the session.

The 12 mg/kg dose, induced lower overall response rates in HF11 and HF8, than the 8 mg/kg dose level. For HF11, under fixed ratio and variable interval conditions, the overall response rates were slightly decreased from those observed with the 16 mg/kg dosage of the first series, as would be expected. This was not true for HF8. Rat HF8 displayed an overall higher response rate with the 12 mg/kg dosage than that obtained with the 16 mg/kg dosage in the first series of determinations. Average shocks during the second series drug phase under FR conditions, are somewhat reduced from those of the first series with a considerably smaller range. Largest increases in response rate, under fixed ratio and V.I. condition, were observed during the fourth forty minute period for HF8. This is contrary to the 4 mg/kg doses and 8 mg/kg doses where maximum rate increases occur in the third period, immediately following the administration of the drug.

Overall rate increases, for both subjects, lasted into the fifth period of the session at the 12 mg/kg dose level.

Figure 30

Cumulative records showing the results of the administration of methylphenidate at the 4 mg/kg dose level on FR 5 and VI 4 min. baselines. Arrows show point at which injections (i.p.) were given. Records show 3rd and 4th forty minute periods of the session. Oblique pips on records denote shocks. Rats HF11 and HF8. (Note the absence of shock clusters following drug administration. Compare with Figures 18, 20 and 22).

HF11 rs 20

4mg./kg.

fig.30



HF8 rs 80

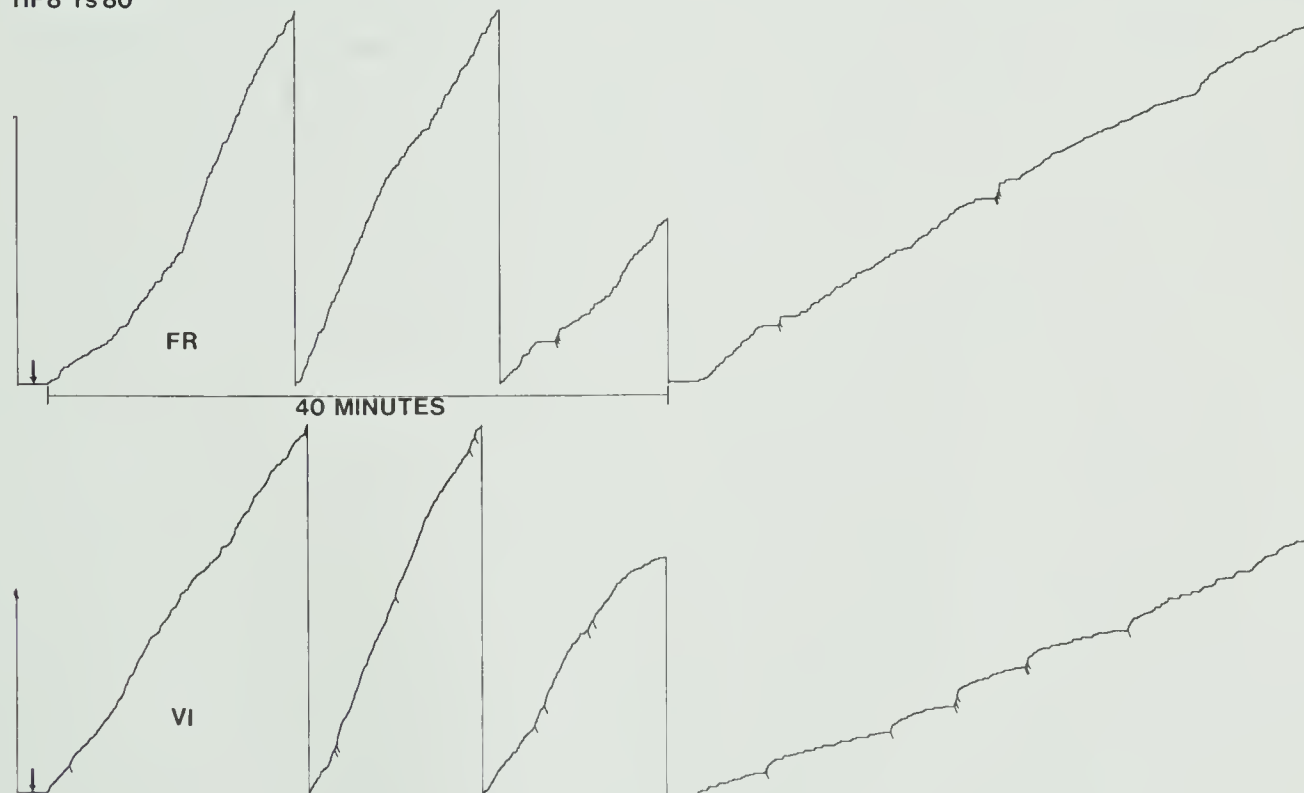


Figure 31

Cumulative records showing the results of the administration of methylphenidate at the 8 mg/kg dose level on FR 5 and VI 4 min. baselines. Arrows show points of injections. Records show 3rd and 4th forty minute periods of the session. Oblique pips denote shocks. Rats HF11 and HF8.

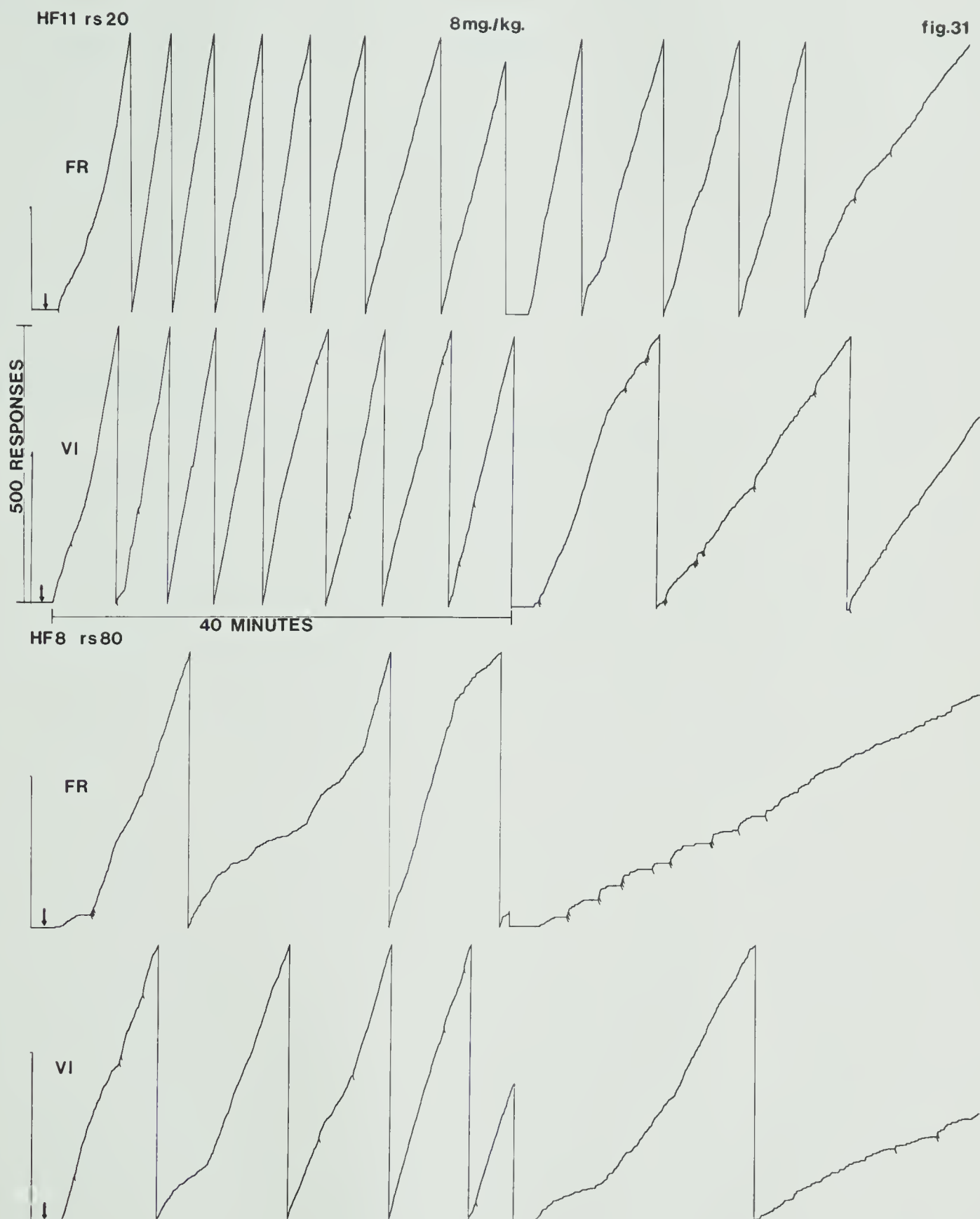


Figure 32

Cumulative records showing the results of the administration of methylphenidate at the 12 mg/kg dose level on FR 5 and VI 4 min. baselines. Arrows show points of injections. Records show 3rd and 4th forty minute periods of the session. Oblique pips denote shocks. Rats HF11 and HF8.

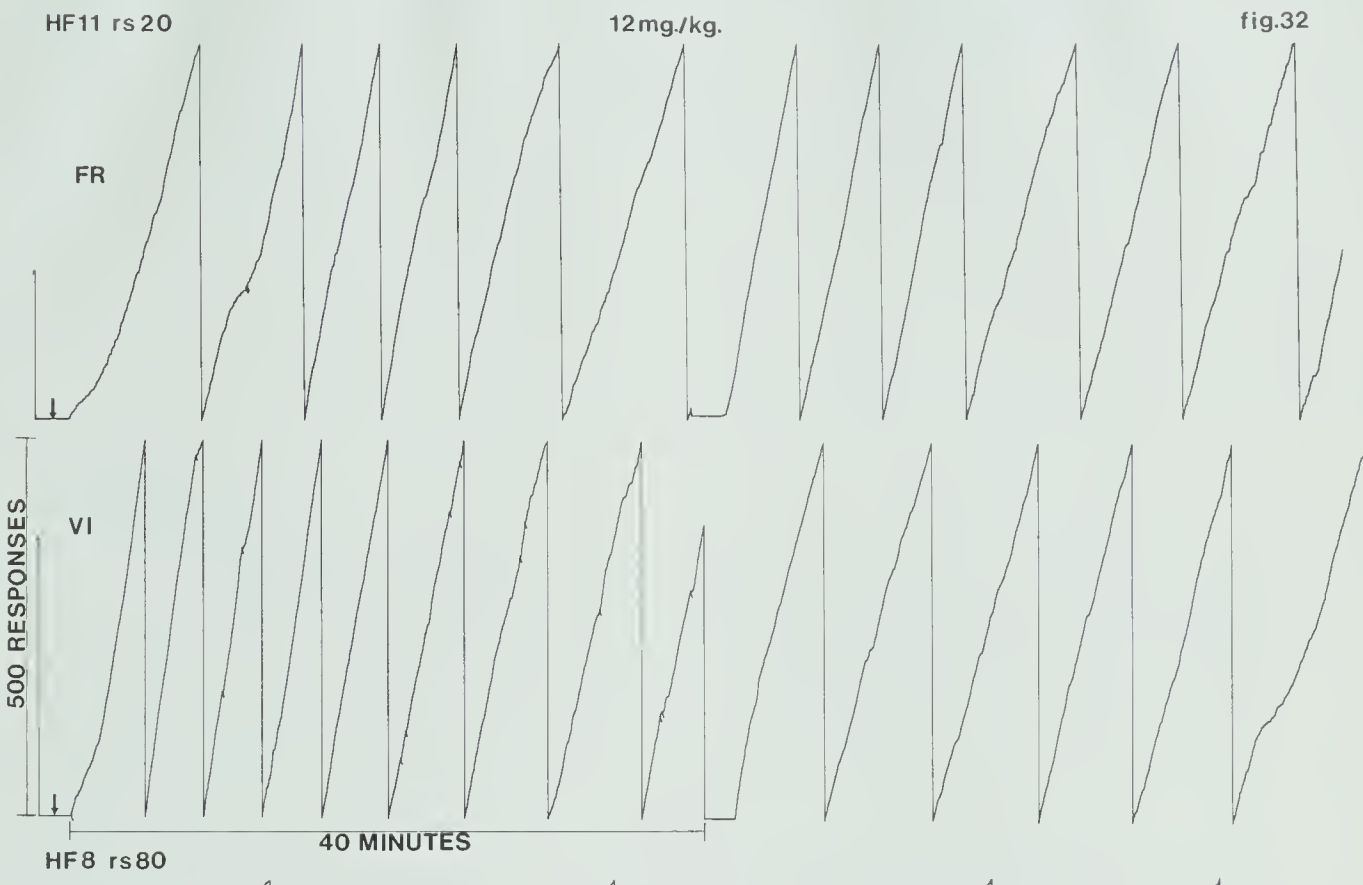


Figure 33

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) under isotonic saline conditions. (Black indented bars represent variable interval 4 minute shock presentation). Vertical lines represent the range. Rats HF11 and HF8.

saline

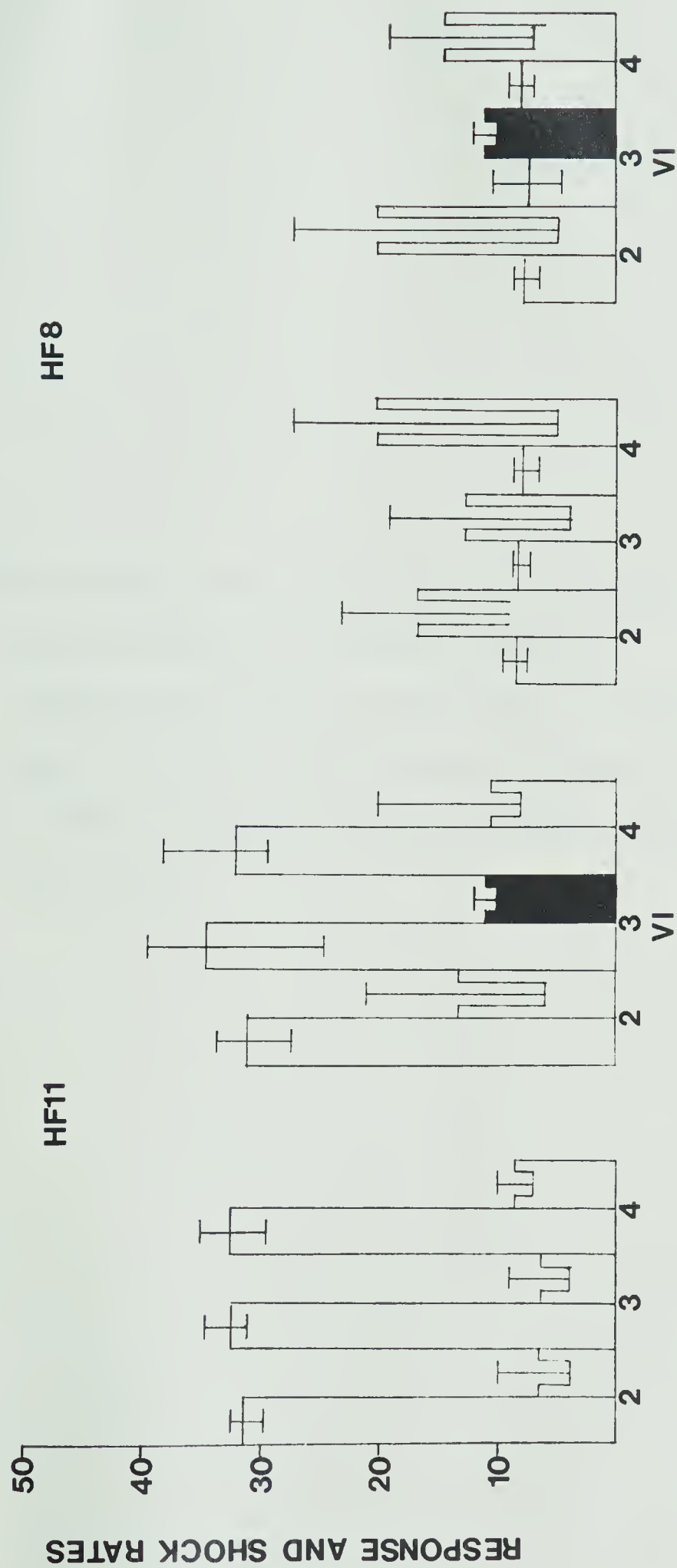
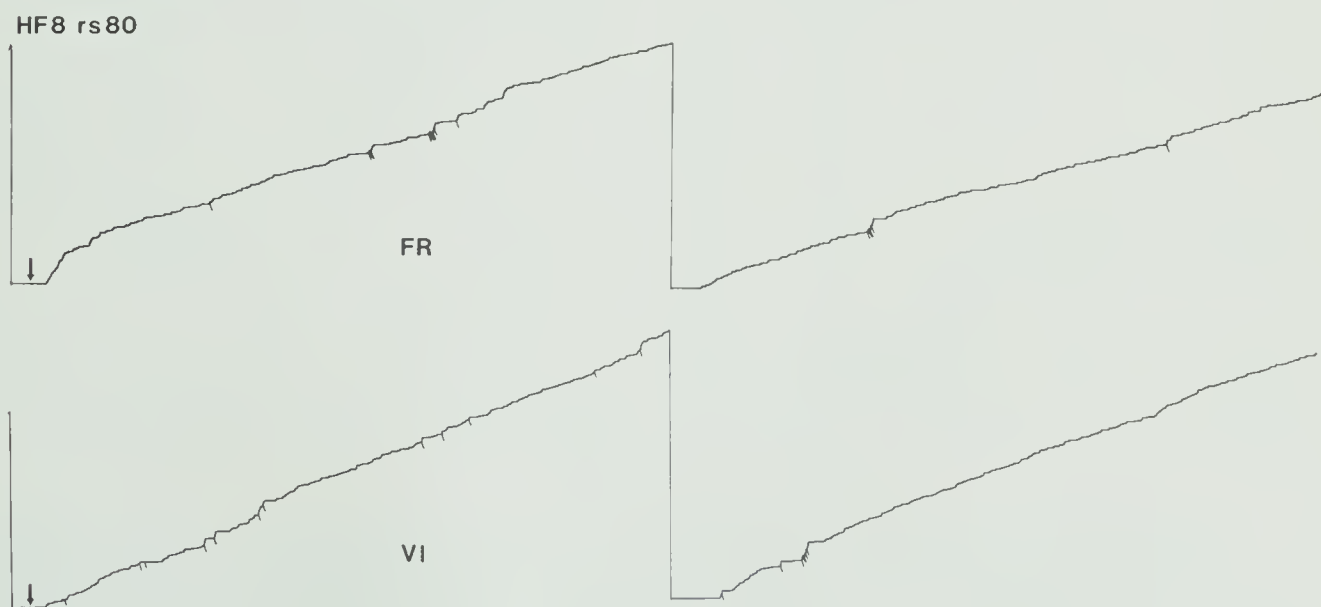
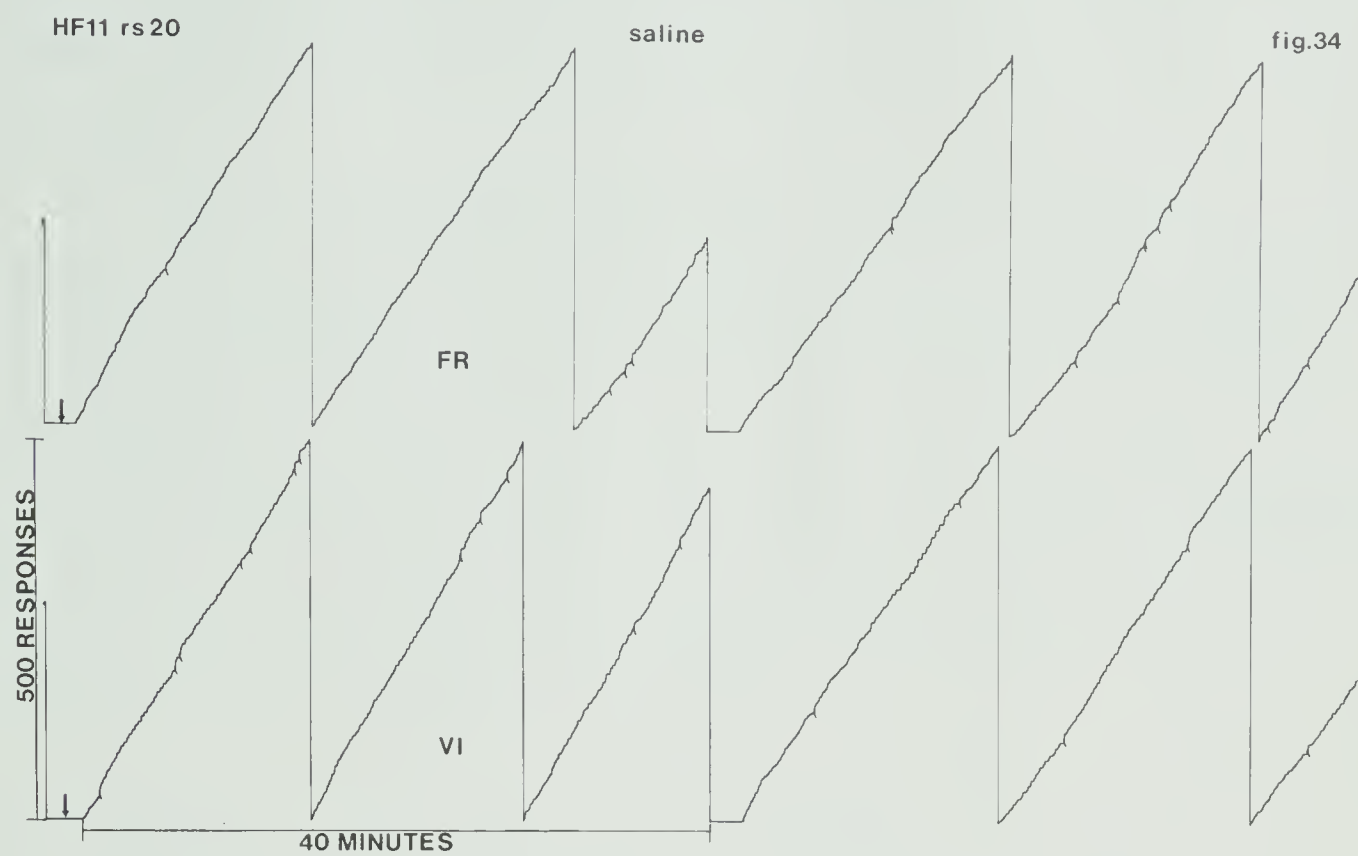


fig.33

40 MINUTE PERIODS

Figure 34

Representative cumulative records showing results of administration of isotonic saline solution. Arrows show point of injection. Records represent the 3rd and 4th forty minute periods of the session. Oblique pips on records denote shocks. Rats HF11 and HF8.



Results of injections of isotonic saline solution (Figures 33 and 34, see also Table 11, in appendices) were consistent with overall response rates observed under fixed ratio and variable interval control conditions.

Dose-effect curves for HF11 and HF8 are shown in Figure 34A. Both subjects show similar drug-induced effects under both FR and VI conditions. Absolute rate increases are greater for HF11, but in terms of the relative behavioral output over baseline control conditions (Figure 34B, and Table II) subject HF8, the low rate animal, shows a greater increase.

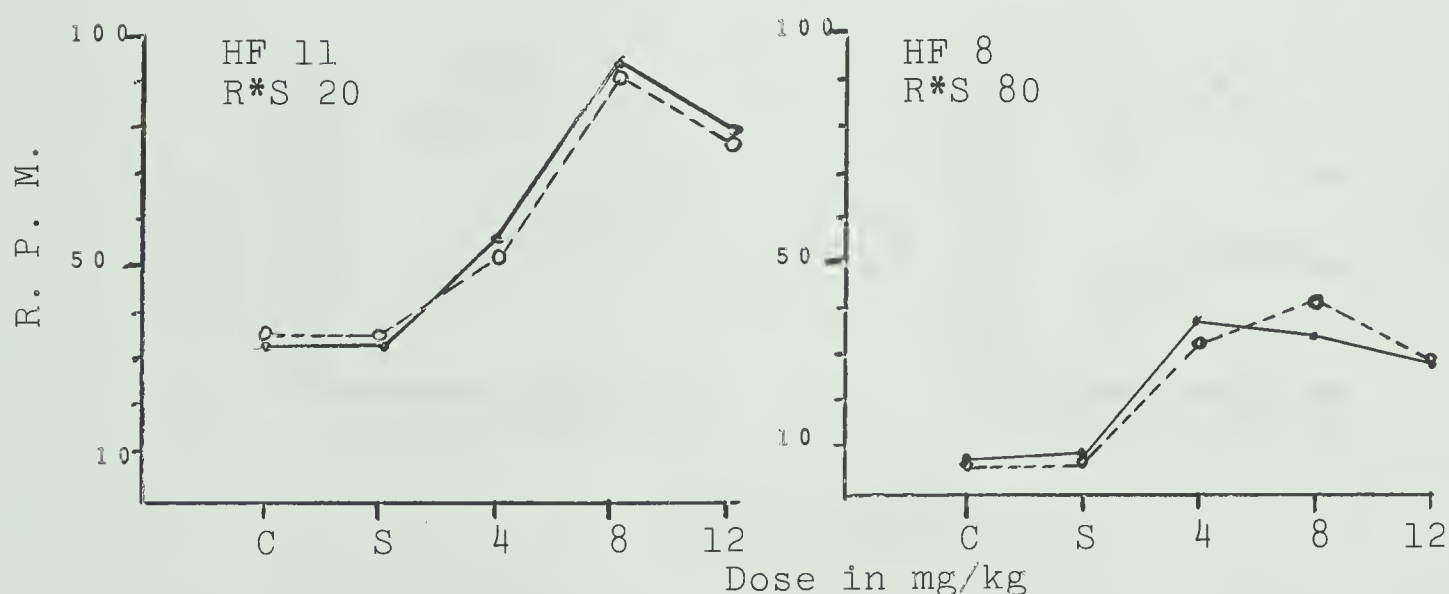


Figure 34A. The effects of methylphenidate on rate of responding on FR 5 (solid line) and VI 4' shock presentation (dotted line). The points above "C" show the non-injection control rates. The points above "S" show the rate after saline injections. The points for each dosage are the mean of four observations. Data represents the third period of the experimental session.

Maximum rate increasing effects appear at the 8 mg/kg dose level, with the exception of HF8, which shows maximum effects under FR conditions occurring at the 4 mg/kg dose level.

TABLE II

Subjects	4 mg/kg	8 mg/kg	12 mg/kg
HF 11 R*S 20 FR	1.71	2.90	2.50
HF 8 R*S 80 FR	4.62	4.25	3.37
HF 11 R*S 20 VI	1.40	2.51	2.08
HF 8 R*S 80 VI	4.12	5.25	3.62

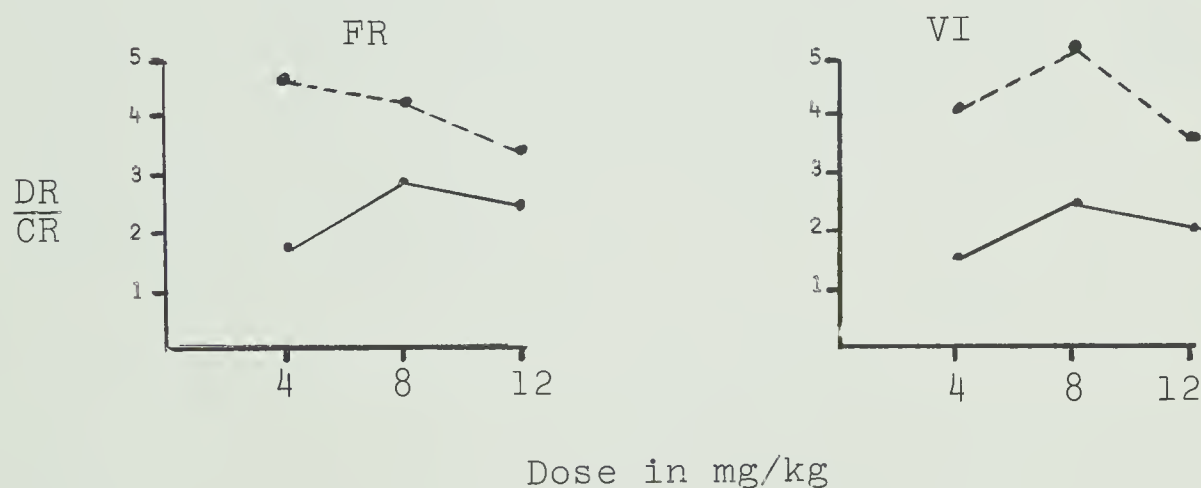
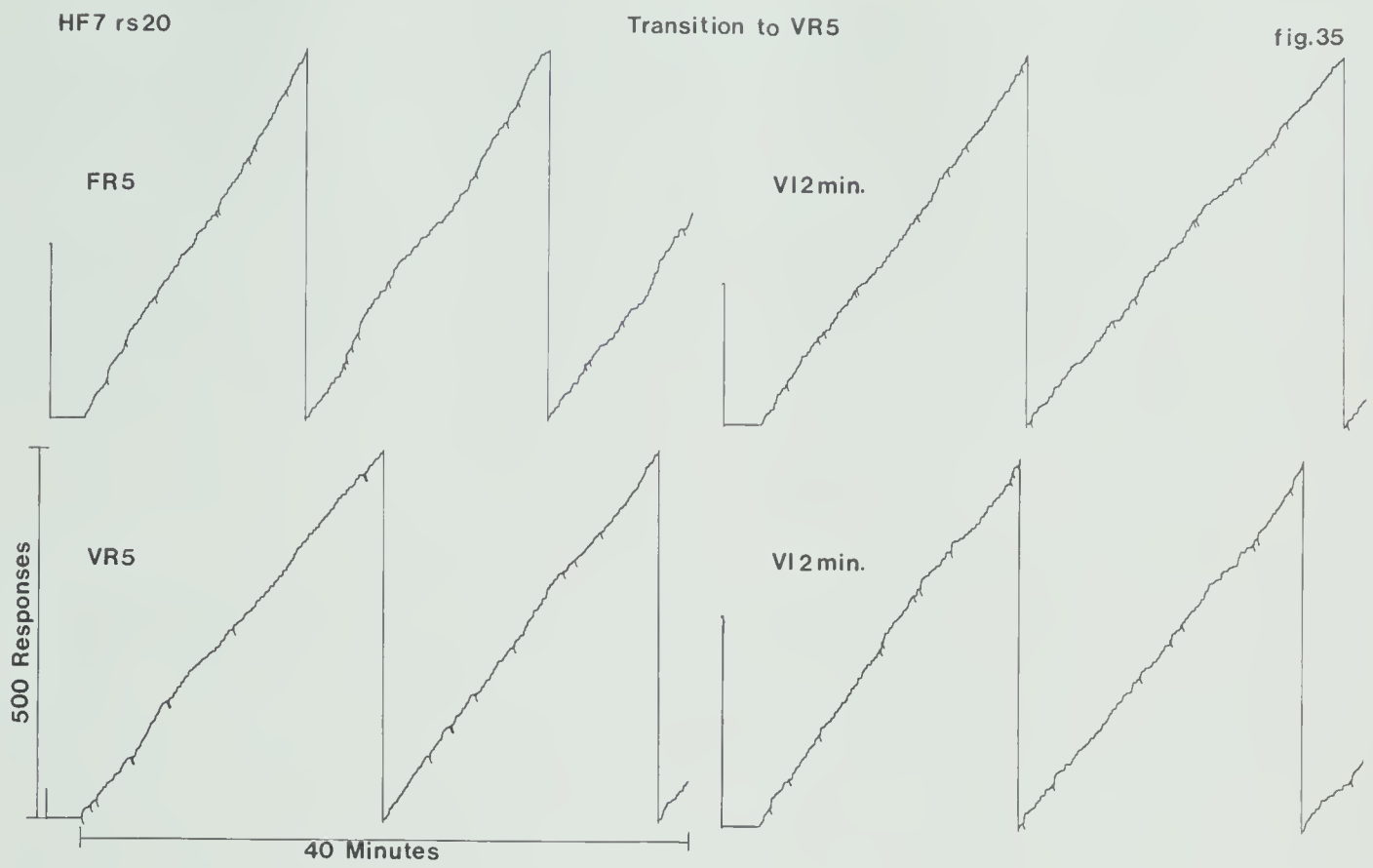


Figure 34B. Relative ratio increases in behavioral output over baseline control rates in the individual subjects HF8 (dotted line) and HF11 (solid line). Points represent the mean of four observations divided by their respective baseline control rates.

In summary, the results of the second series of drug tests were found to be very similar for a given animal on both FR 5 avoidance behavior and on behavior maintained by variable interval presentation of unavoidable shocks, ie., when shock frequency was common to both animals of the R*S 20 sec. - R*S 80 sec. pair. This similarity in effect was observed for all three (4, 8 and 12 mg/kg) of the doses administered.

Figure 35

Representative cumulative records showing transition from FR 5 to VR 5 avoidance baselines. Records show the third 40 min. period of the experimental session. Oblique pips denote shocks. Note the reduction in shock frequency in Rat HF4 on VR 5 baseline; reduction in response rates under VR 5 and VI 2 min. conditions is also evident. Rats HF7 and HF4.



(v) Paired variable ratio/variable interval
restabilization

At the start of the second series of drug determinations one pair of subjects (HF7 and HF4) showed appreciable instability in their fixed ratio avoidance baselines. Examination of the cumulative records in Figure 35 reveals an increasing tendency toward shock-elicited responding throughout the experimental session. This is particularly evident in the records of animal HF4. Rat HF4, under the R*S 80 sec. parameter, primarily displayed shock-elicited responding, that is rather than responding continuously during the response-shock interval to delay shock, the animal customarily escaped from consecutive shock deliveries programmed by the shock-shock interval. This characteristic of performance was accentuated by the FR requirement. If the animal did not emit the ratio requirement during the 80 second R*S interval, a shock occurs which resets the FR requirement to five. Thus, the animal must satisfy the ratio requirement within the 5 second S*S interval in order to terminate the shocks. Under these conditions shock, rather than being supportive to avoidance responding, takes on the aversive characteristics of a punishing stimulus, producing a deterioration in responding. Figure 36 amply testifies to the difficulties encountered by the R*S 80 sec. animal, HF4

Figure 36

Overall response rate per minute and average shocks per 40 minute period for the third period of the experimental session for 20 consecutive FR/VI sessions and 10 consecutive VR/VI sessions. Rat HF4.

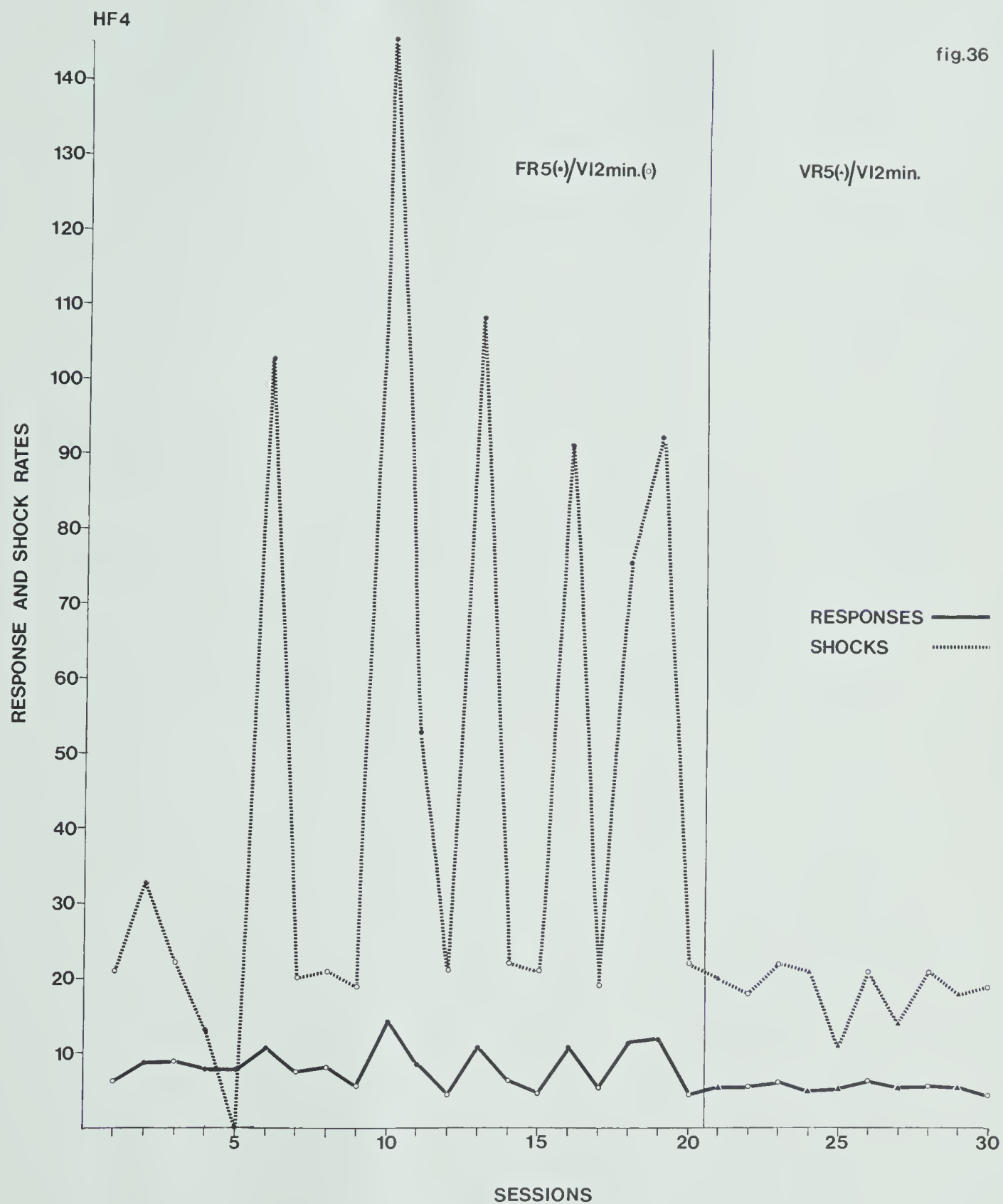


Figure 37

Overall response rate per minute and average shocks per 40 minute period for the third period of the experimental session for 20 consecutive FR/VI sessions and 10 consecutive VR/VI sessions. Rat HF7.

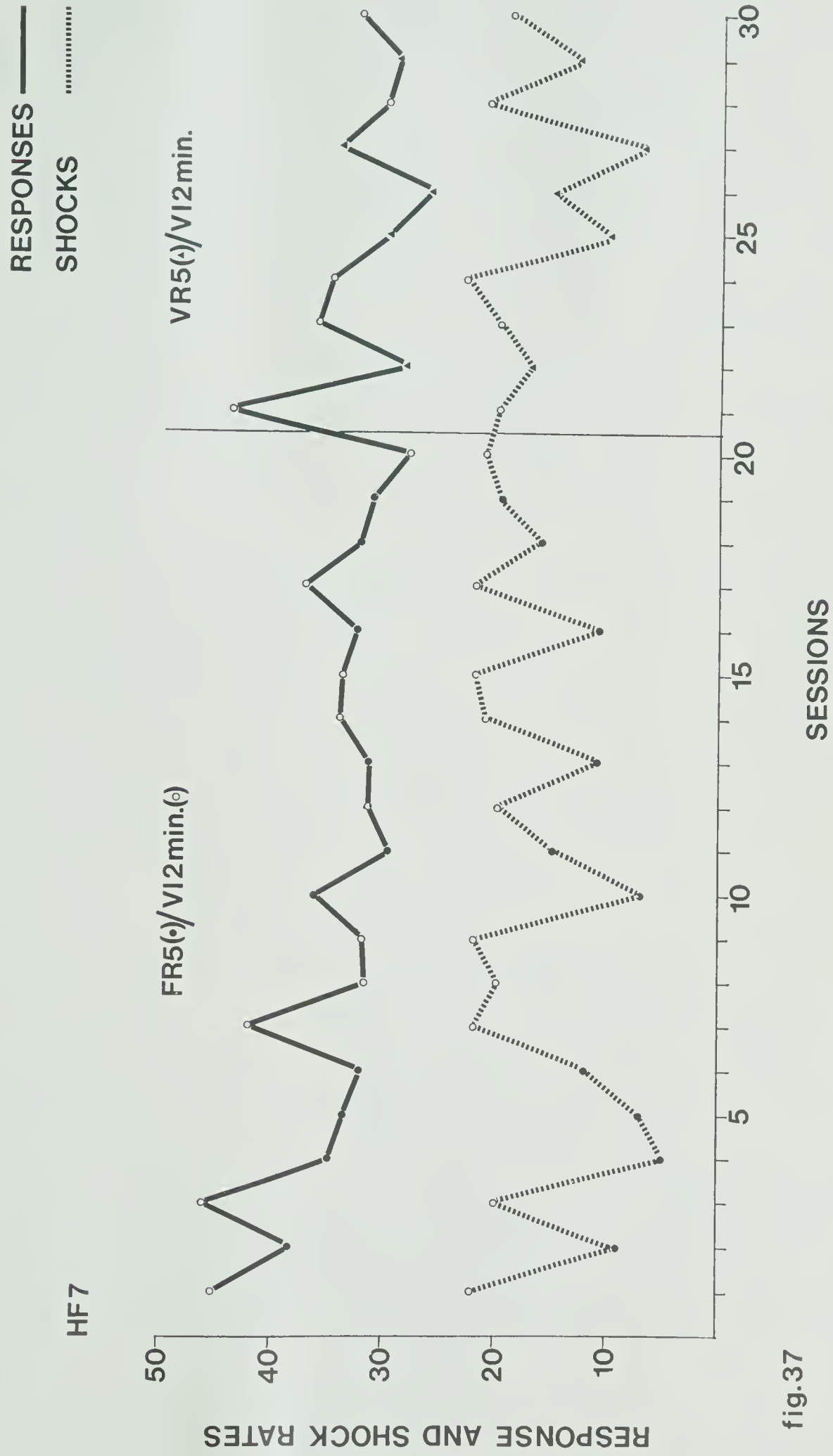


fig.37

on the FR schedule. Particularly evident is the stable pattern of responding, (last 10 sessions in Figure 36), and the large reduction in shock rate per 40 minute period (last 10 sessions in Figure 36) emerging under the variable ratio/variable interval conditions. Rat HF7 on the R*S 20 sec. parameter did not encounter this problem to the same degree (Figure 37).

For this pair of animals, then, a further procedural modification was made, in order to reestablish an avoidance baseline. The schedule parameters remained the same for both animals while the number of responses required to avoid shock was changed to a modified variable ratio of five responses. Under this condition the subjects were required to make, on average, five responses to avoid shock. Results of the restabilization under this condition are shown in Figure 38. Rat HF4 now displays a lower overall rate of responding and a much lower shock frequency. Overall rate of responding is slightly decreased for HF7 over baseline response rates engendered by the FR 5 condition. Baseline shock rates, however, are increased over those observed under the FR 5 condition. (See Table 12, in appendices). Results of the variable interval period are similar to those observed during the variable ratio periods for both sub-

Figure 38

Overall response rate per minute (solid bars) and average shock rate per 40 minute period (indented bars) under VR 5/VI 2 min. control conditions. (Black indented bars represent variable interval 2 min. shock presentation). Vertical lines represent the range. Rats HF7 and HF4.

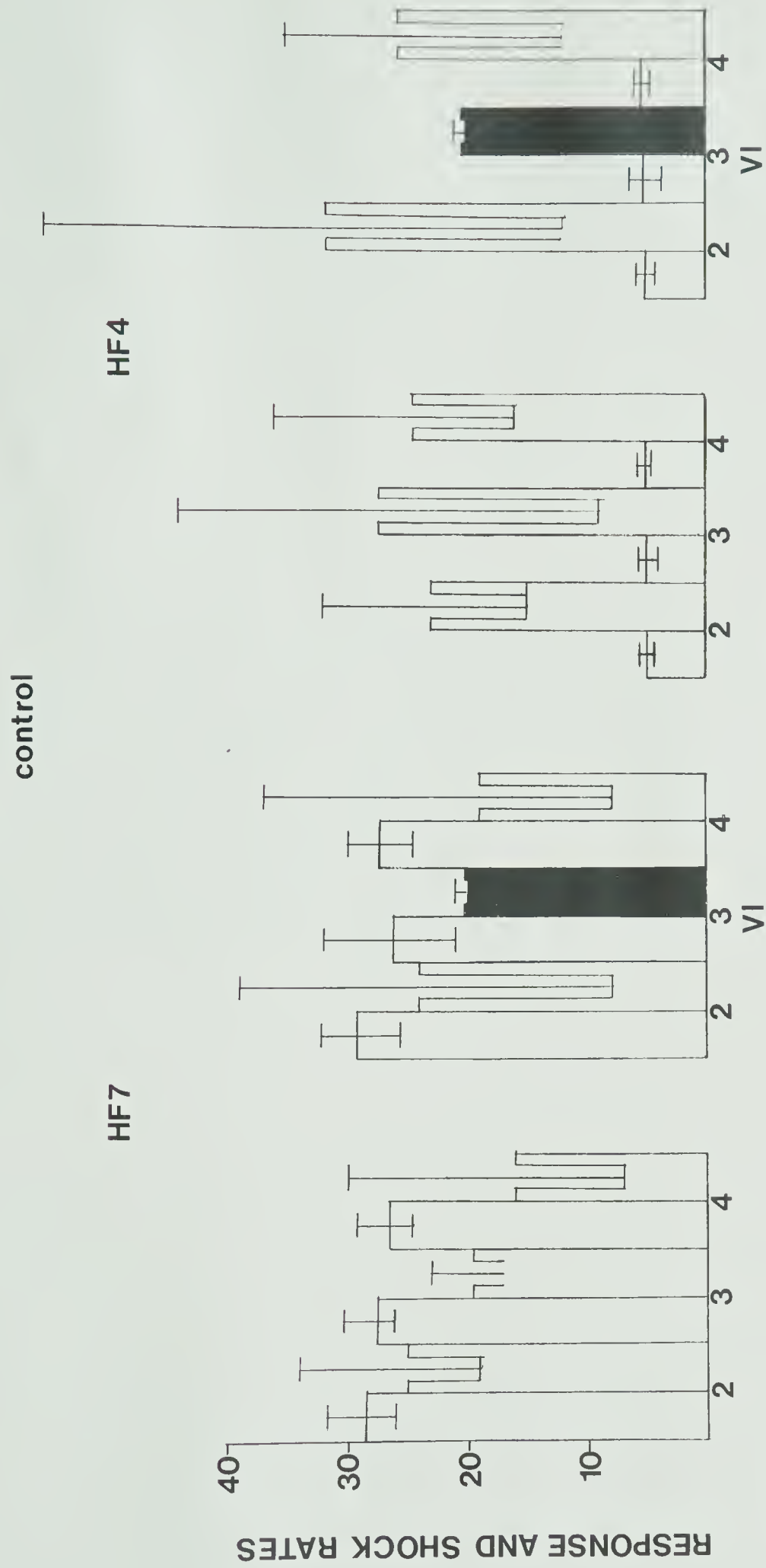
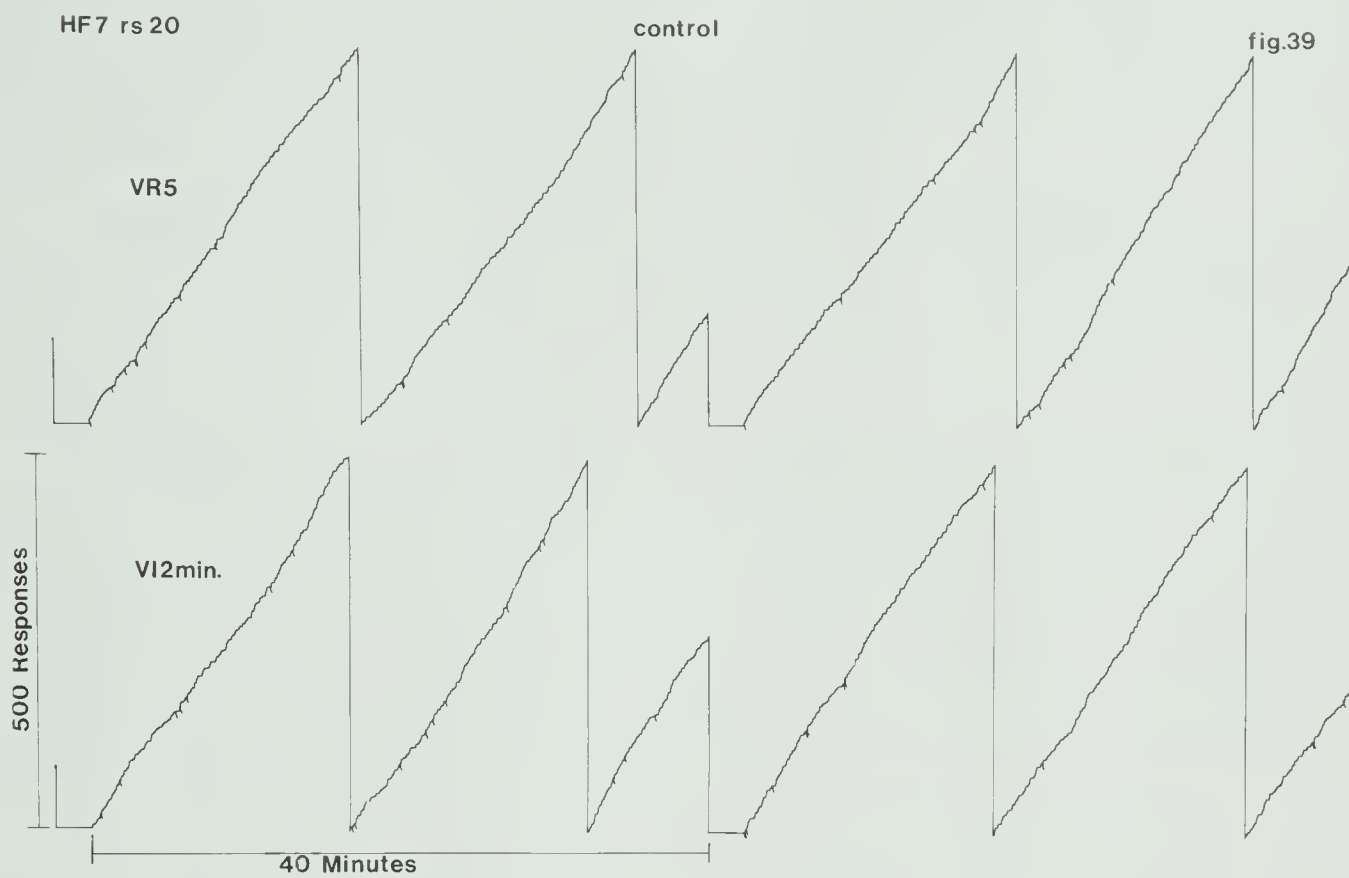


fig.38

Figure 39

Representative cumulative records showing VR 5 and VI 2 min. control baselines. Note the similarity in response and shock rates between VR and VI periods. Oblique pips on the records denote shocks. Records represent 3rd and 4th forty minute periods of the session. Rats HF7 and HF4.



jects (Figure 39). Overall response rates per minute were decreased as compared to HF11 and HF8 while the average number of shocks per 40 minute period were considerably increased as compared to the fixed ratio pair. Overall shock frequency, under variable ratio conditions, was very similar for rats HF7 and HF4.

Restabilization, under variable ratio/variable interval conditions, was obtained within ten experimental sessions.

Throughout this phase of the experiment HF7 and HF4 maintained very stable baseline response rates under control conditions, however, shock frequency fluctuated over a sizeable range. This was especially true in the case of HF4 (Figure 39).

(vi) Findings emerging from the third series of drug determinations

Results of the 4, 8 and 12 mg/kg determinations are shown in Figures 40, 41 and 42 respectively. (See also Tables 13, 14 and 15, in appendices). Representative cumulative records are presented in Figures 43, 44 and 45.

Under variable ratio conditions Rat HF7 displayed a monotonic increase in baseline response rate (over control rates) as a function of the increase in the size of the dose of methylphenidate administered. Baseline

Figure 40

Overall response rate per minute (solid bars) and average shocks per 40 minute period (indented bars) for four determinations of methylphenidate at the 4 mg/kg dose level. (Black indented bars represent variable interval 2 min. shock presentation). Vertical lines represent the range. Rats HF7 and HF4.

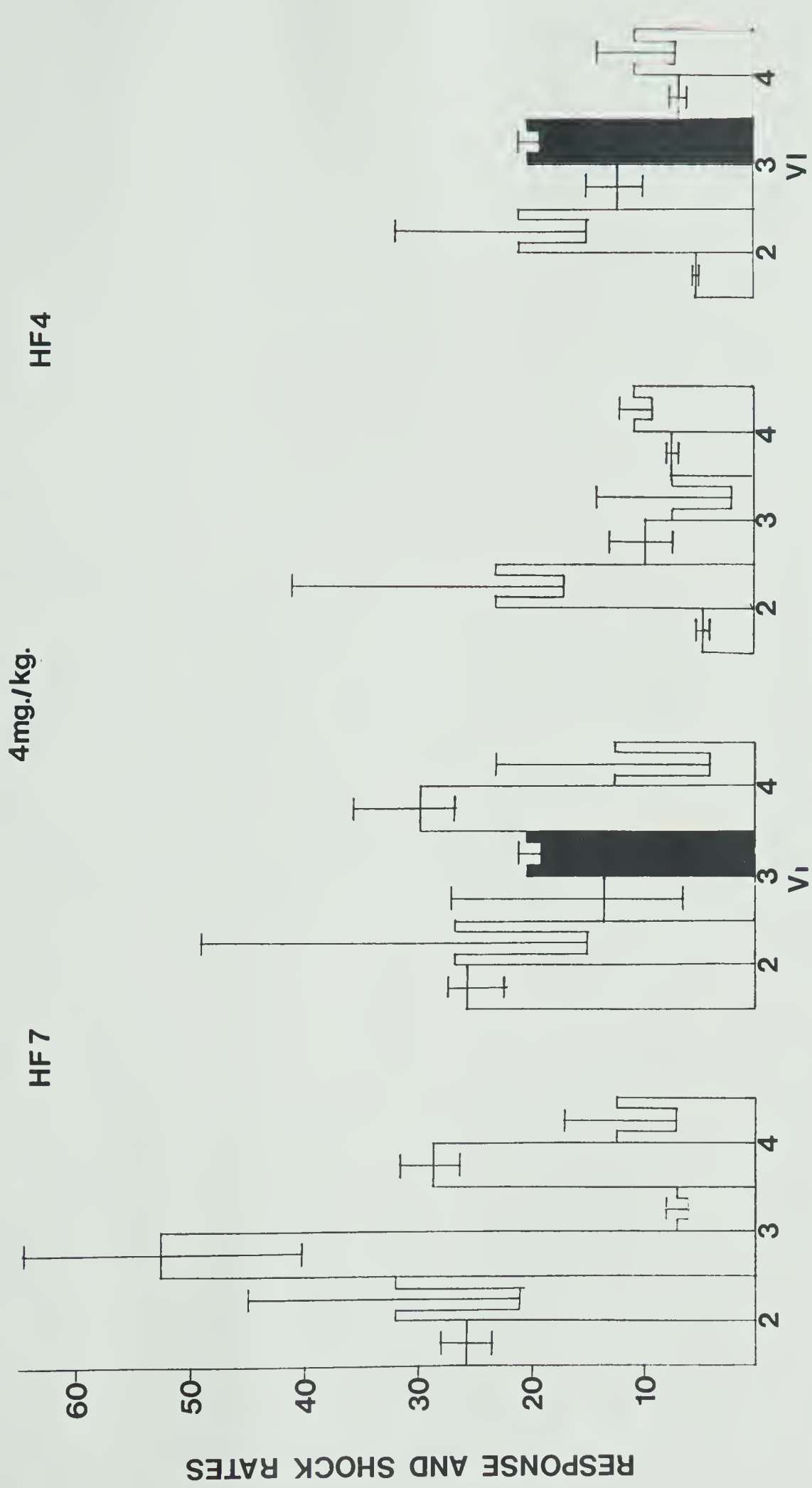


fig.40

Figure 41

Overall response rate per minute (closed bars) and average shock rate per 40 minute period (indented bars) for four determinations of methylphenidate at the 8 mg/kg dose level. (Black indented bars represent variable interval 2 min. shock presentation). Vertical lines represent the range. Rats HF7 and HF4.

8mg./kg.

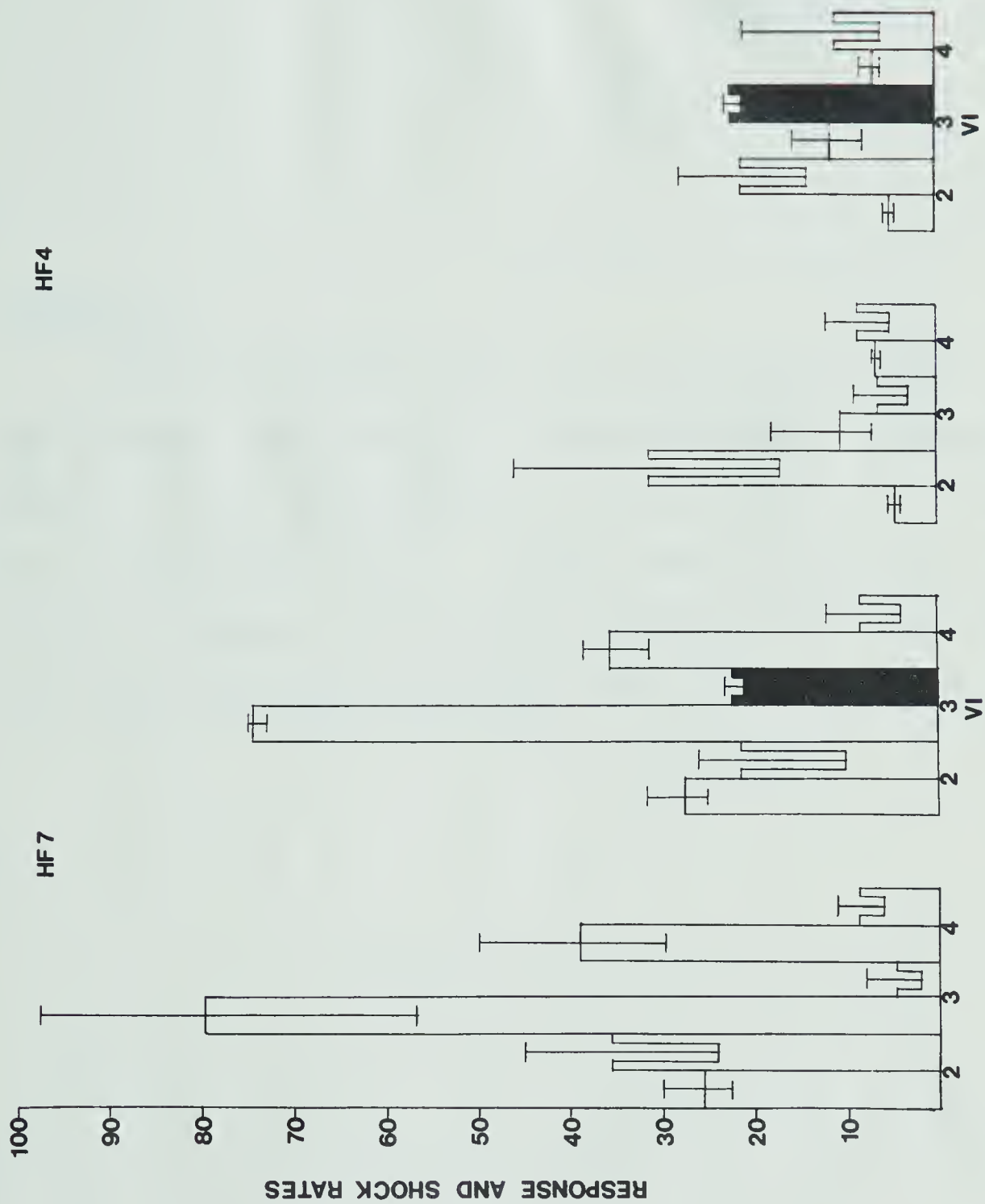


Figure 42

Overall response rate per minute (solid bars) and average shock rate per 40 minute period (indented bars) for four determinations of methylphenidate at the 12 mg/kg dose level. (Black indented bars represent variable interval shock presentation). Vertical lines represent the range. Rats HF7 and HF4.

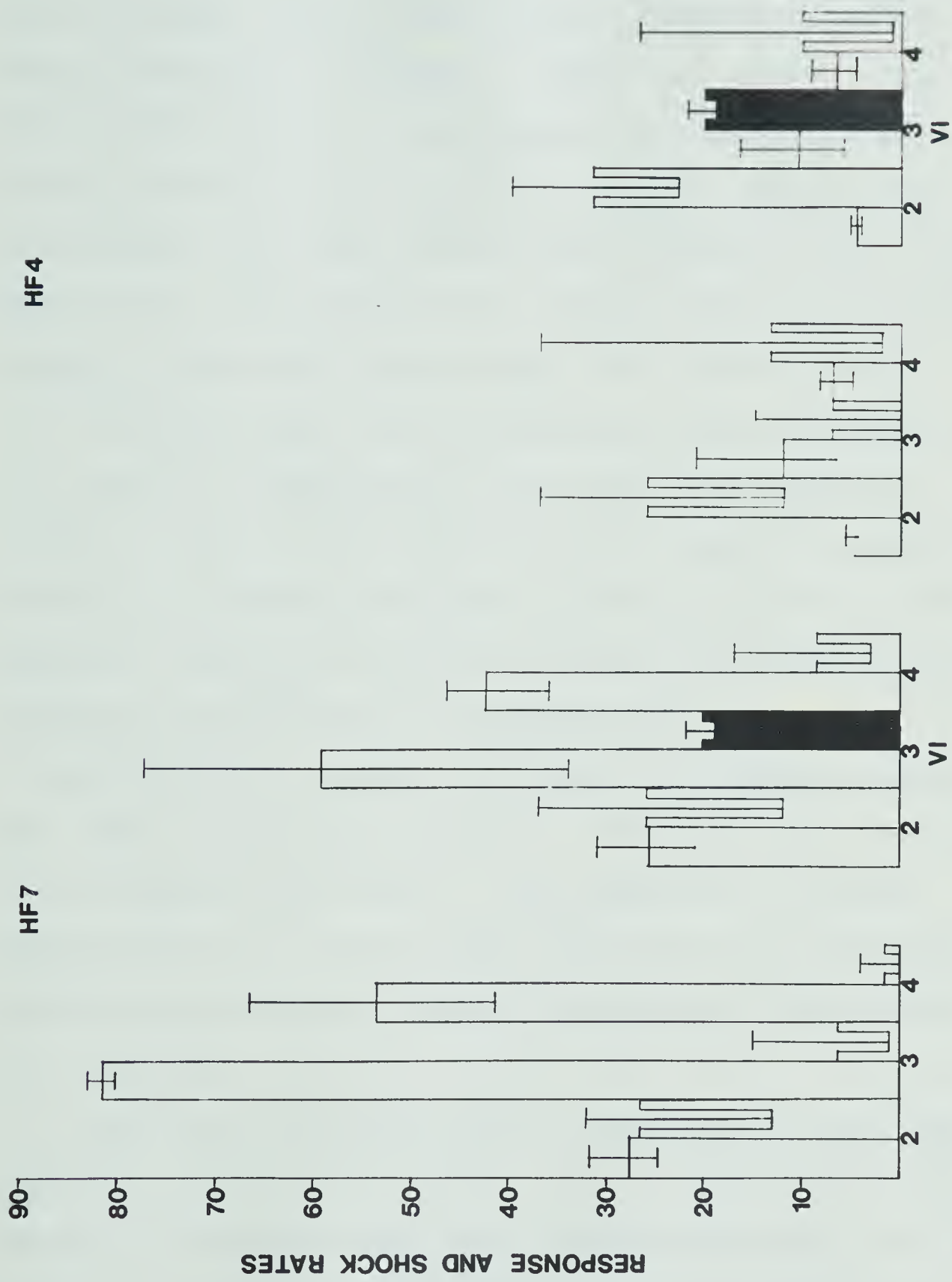


fig.42

40 MINUTE PERIODS

shock rates, under drug conditions (3rd and 4th 40 minute periods are consistently reduced from shock rates observed under control conditions. Variable interval results are quite different. Under V.I. control conditions HF7 showed a slight overall tendency to a decrease (from FR control RPM) in baseline response rates (See Figure 38). This decrease was enhanced at the 4 mg/kg dose level. (See Figure 40). Overall rate of responding dropped to the order of one half that observed under control conditions. Shock frequency, under VR conditions at 4 mg/kg is approximately one third that observed during the control VR period and the 4 mg/kg VI period, which is of course, the same as during the control period. Under VR conditions the 8 and 12 mg/kg are very similar differing essentially in the greater duration of the 12 mg/kg effect. Largest increments in response rates and least variability under V.I. conditions were produced by the 8 mg/kg dose level. (See Figure 41). Overall rate increases at the 12 mg/kg dose level were moderate to near control rates showing considerable range during V.I. periods.

Rat HF4, on the other hand, displayed moderate rate increases, relative to control rates, engendered by each dosage. Consistent with those findings emerging from HF7, under V.R. conditions, HF4 shows an overall monotonic

increase in baseline response rate as a function of increasing dosage. Variability, as seen in the ranges, also increases with increasing dosage. This trend is reversed under V.I. conditions as far as overall rate increases are concerned. Largest overall increments in response rates are engendered by the 4 mg/kg dose, thereafter, decreasing as a function of increasing dosage. Greater variability is observed at the 12 mg/kg dosage as compared with the 4 mg/kg dosage.

Another observation from HF4, differing from HF7, relates to the duration of drug effects. Drug-induced rate increases for HF4 did not persist as a function of the dose given under either the variable ratio or variable interval sessions. Overall response rates per minute and average shock rates during the fourth period of both VR and VI drug sessions are almost identical for all three dosages administered.

Dose-effect curves for HF7 and HF4 are shown in Figure 45A. Subject HF7 shows somewhat different effects of the drug at doses of 4 and 12 mg/kg as a function of the VR or VI conditions. Subject HF4, on the other hand, displays consistent dose effect relationships under both VR and VI conditions.

Relative ratio increases in behavioral output (See Table III and Figure 45B) are very similar for both sub-

Figure 43

Representative cumulative records showing the results of administration of methylphenidate at the 4 mg/kg dose level. Small arrows show points of injection. Large arrow shows suppression of responding during VI period. Oblique pips on records denote shocks. Records represent 3rd and 4th forty minute periods of the session. Rats HF7 and HF4.

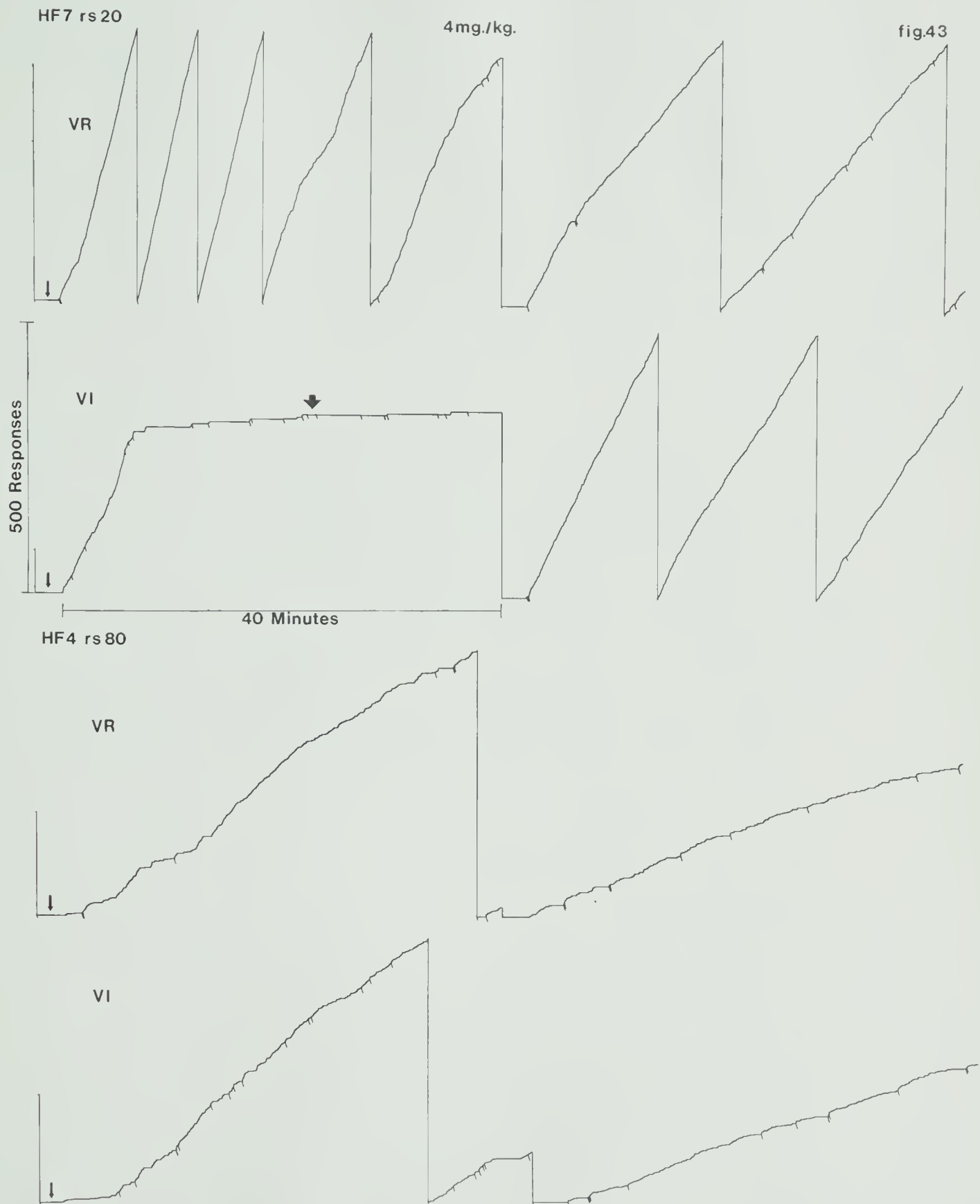


Figure 44

Representative cumulative records showing the results of administration of methylphenidate at the 8 mg/kg dose level. Arrows show points of injection. Oblique pips on records denote shocks. Records represent the 3rd and 4th forty minute periods of the sessions. Rats HF7 and HF4.

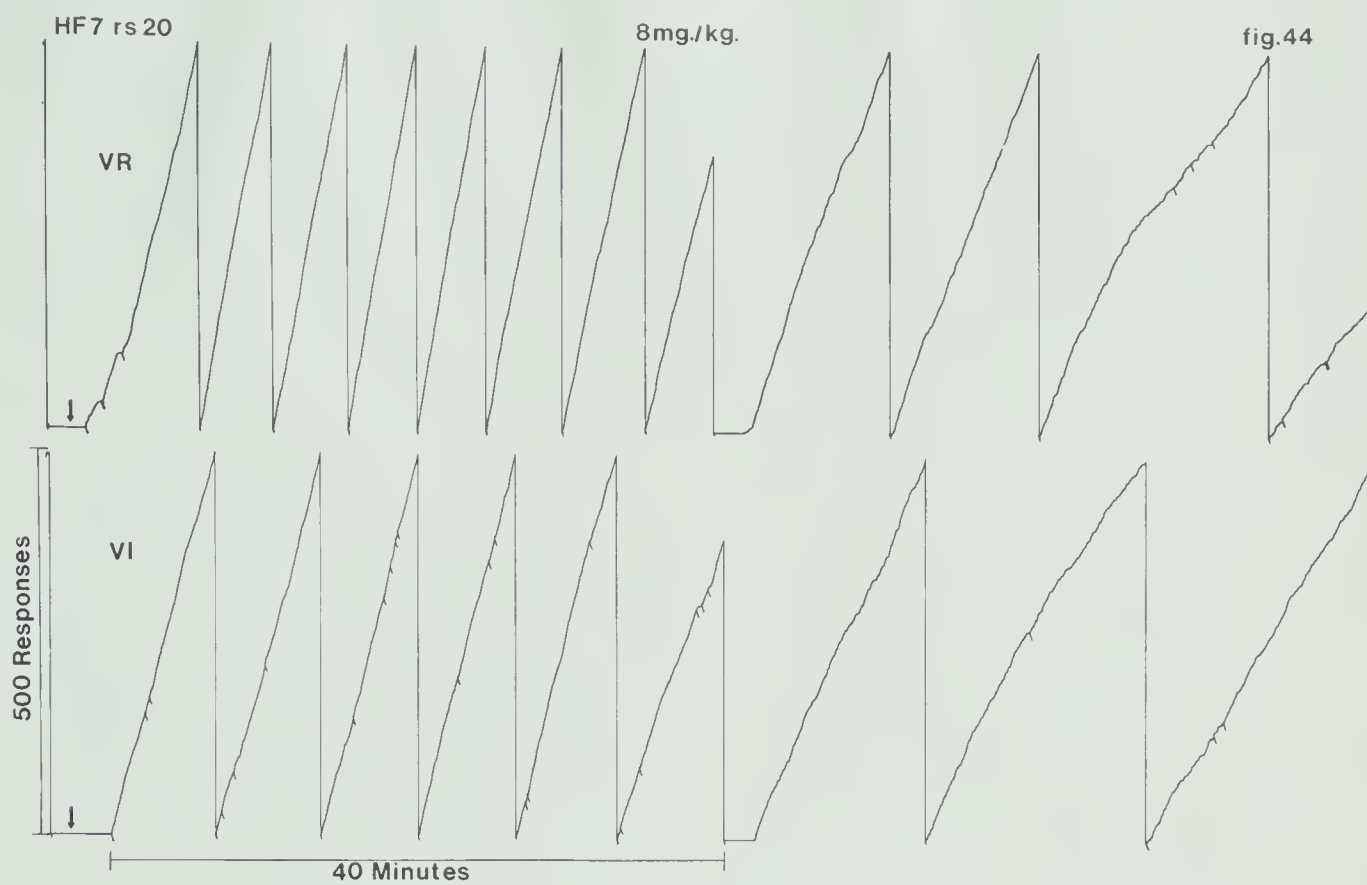
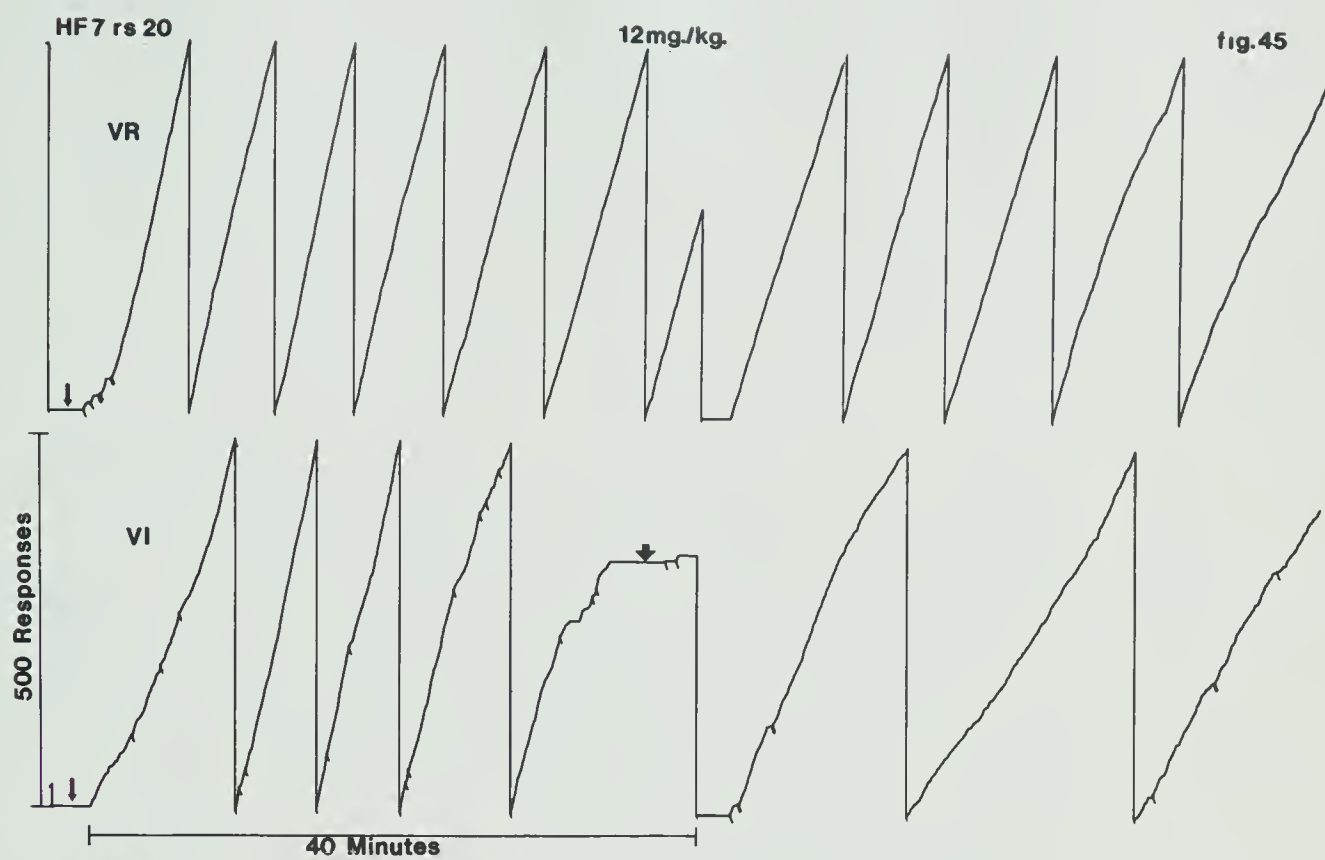


Figure 45

Representative cumulative records showing the results of administration of methylphenidate at the 12 mg/kg dose level. Small arrows show points of injection. Large arrow shows tendency to response suppression. Oblique pips on records denote shocks. Records represent the 3rd and 4th forty minute periods of the session. Rats HF7 and HF4.



HF4 rs 80



Figure 46

Overall response rate per minute (solid bars) and average shock rate per 40 minute period (indented bars) under saline conditions. (Black indented bars represent variable interval 2 min. shock presentation. Vertical lines represent the range. Rats HF7 and HF4.

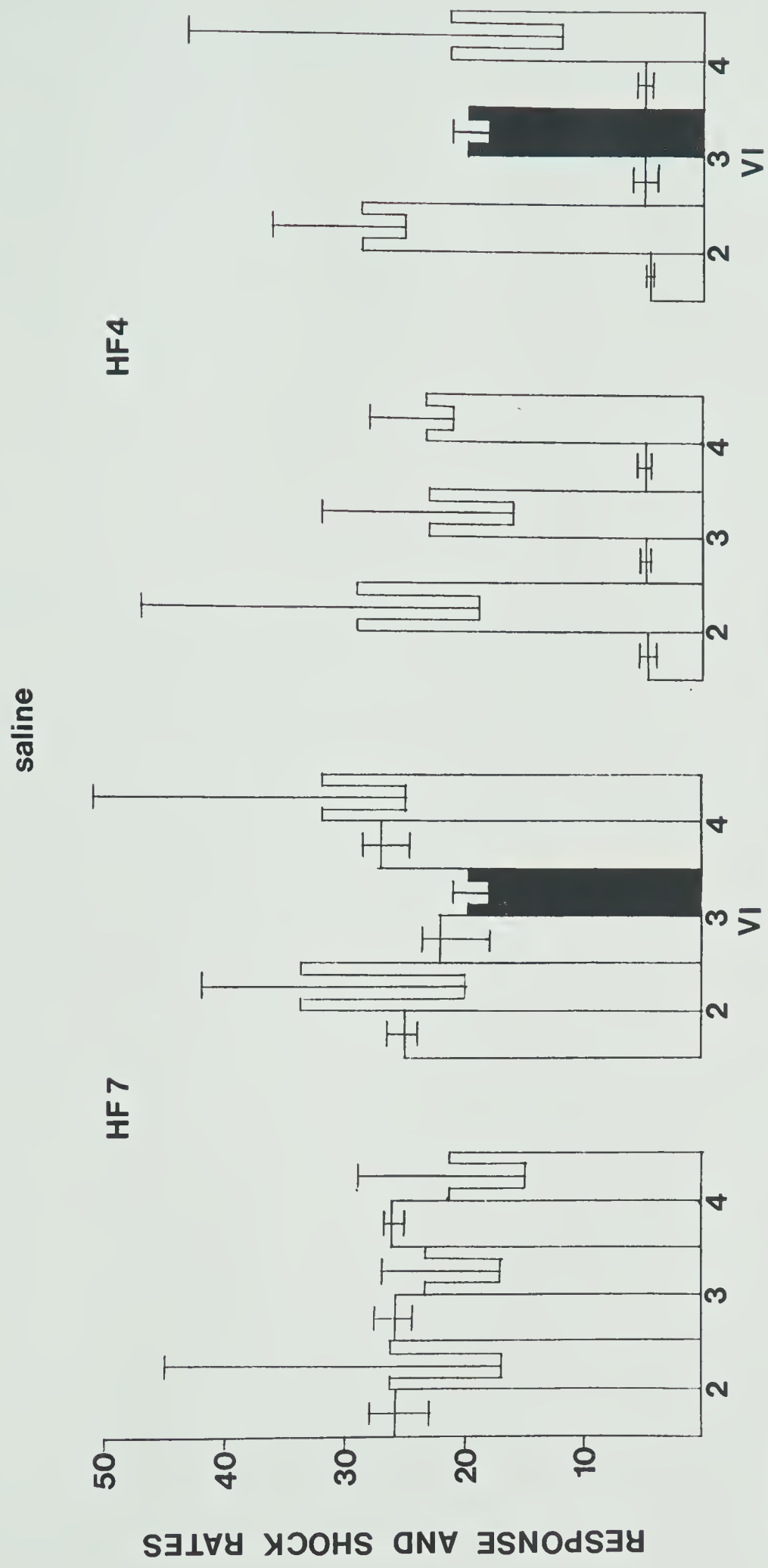


fig.46

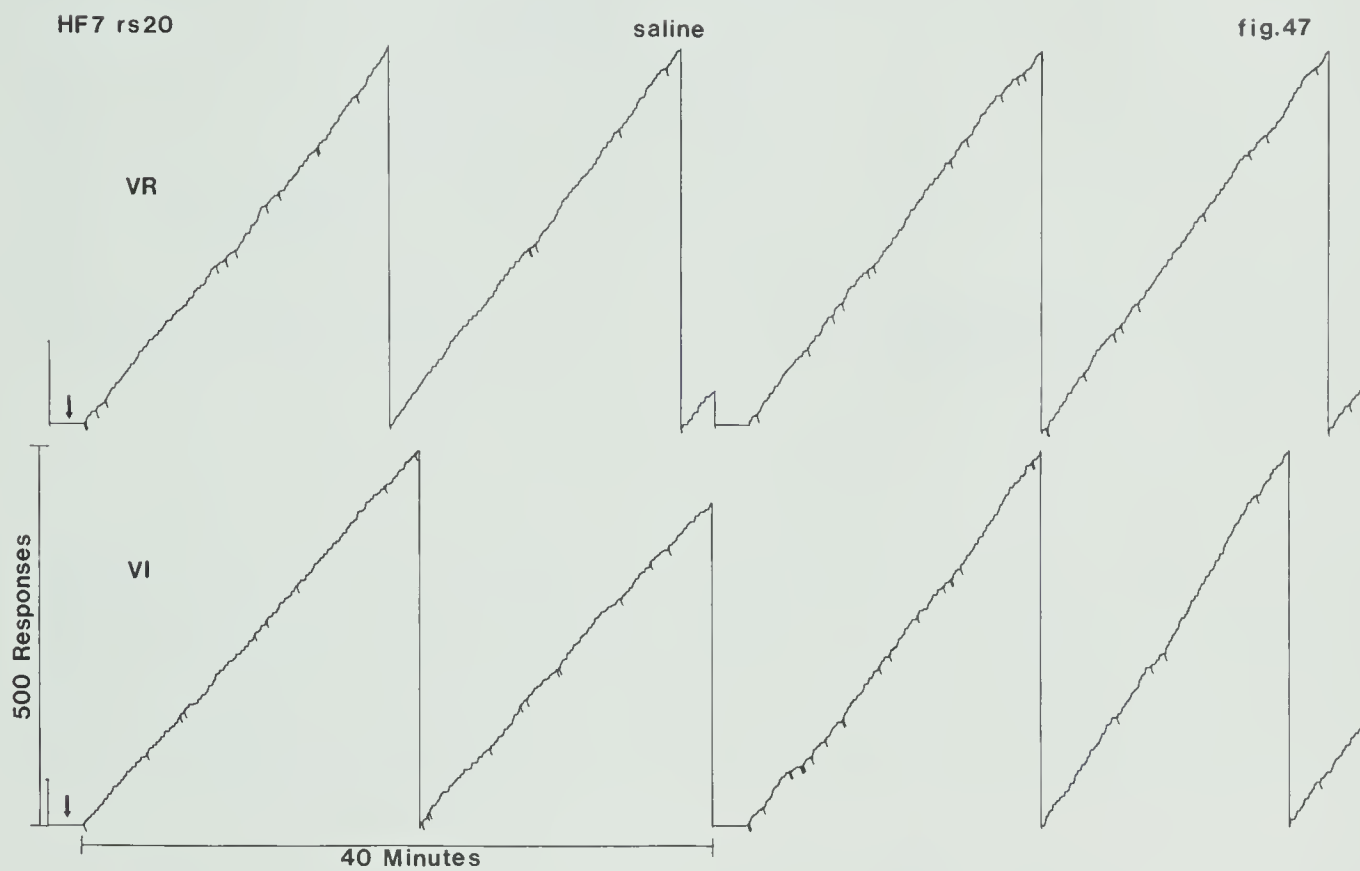
Figure 47

Cumulative records showing the results of administration of isotonic saline solution.

Arrows show points of injections. Oblique pips on records denote shocks. Records represent the

3rd and 4th forty minute periods of the session.

Rats HF7 and HF4.



jects with the exception of the 4 mg/kg dose under

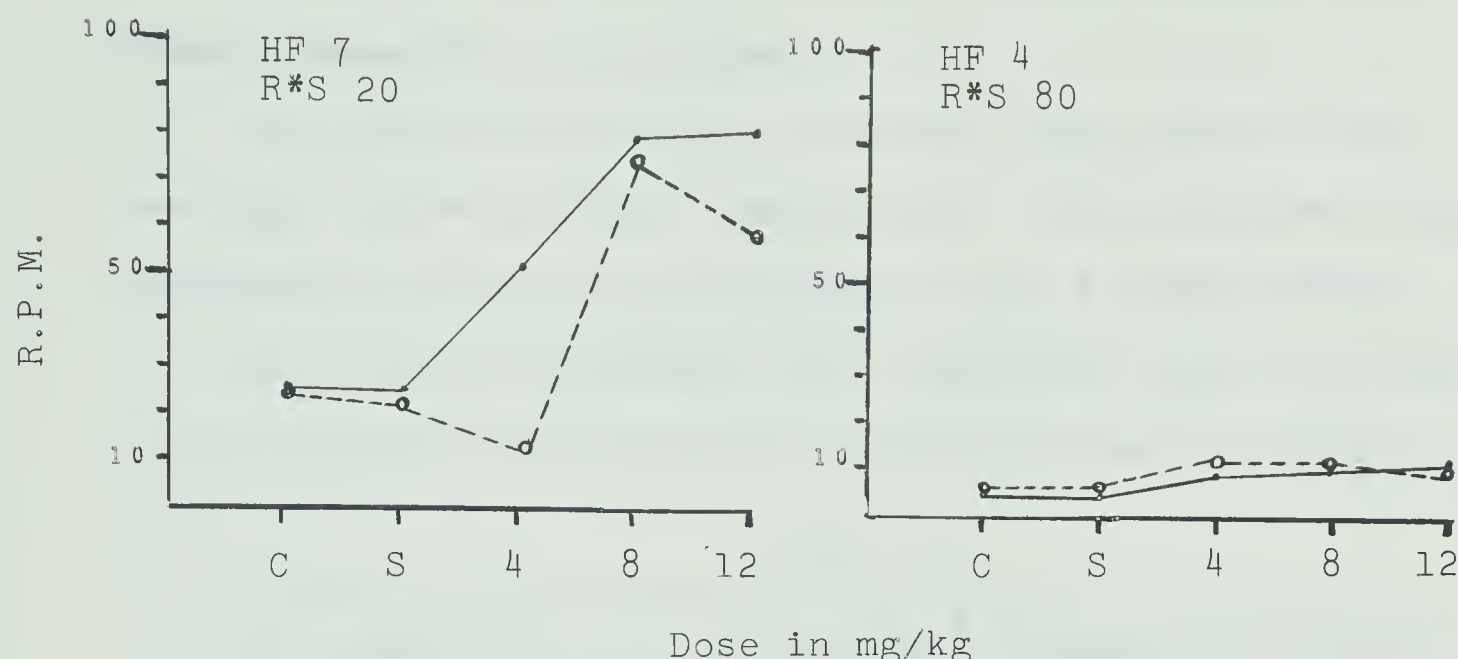


Figure 45A. The effects of methylphenidate on rate of responding on VR (Solid line) and VI 2' shock presentation (dotted line). The points above "C" show the non-injection control rates. The points above "S" show the rate after saline conditions. The points for each dosage are the mean of four observations. Data represents the third period of the experimental session.

V.I. conditions. There is a very slight relative decrease in the R*S 20 sec. subject HF7.

Response rates engendered by control and saline conditions were very similar during VR and VI periods, with the exception of HF7 who showed a slight decrease in response rate under the VI saline conditions. (See Figure 46 and cumulative records in Figure 47; see also Table 16, in appendices).

The following points summarize the main findings of the third series of drug tests:

1. The R*S 20 animal (HF7) displayed moderate monotonic rate increases as a function of the increase in dosage under VR 5 conditions.

2. HF7 did not show a monotonic drug effect under variable interval shock presentation. This is particularly evident in the low response rate at the 4 mg/kg dosage.

3. The R*S 80 animal (HF4) displayed small monotonic rate increases as a function of the increase in dosage

TABLE III

Subjects	4 mg/kg	8 mg/kg	12 mg/kg
HF 7 R*S 20 VR	1.96	2.96	3.04
HF 4 R*S 80 VR	2.00	2.00	2.40
HF 7 R*S 20 VI	0.54	2.88	2.27
HF 4 R*S 80 VI	2.40	2.27	2.14

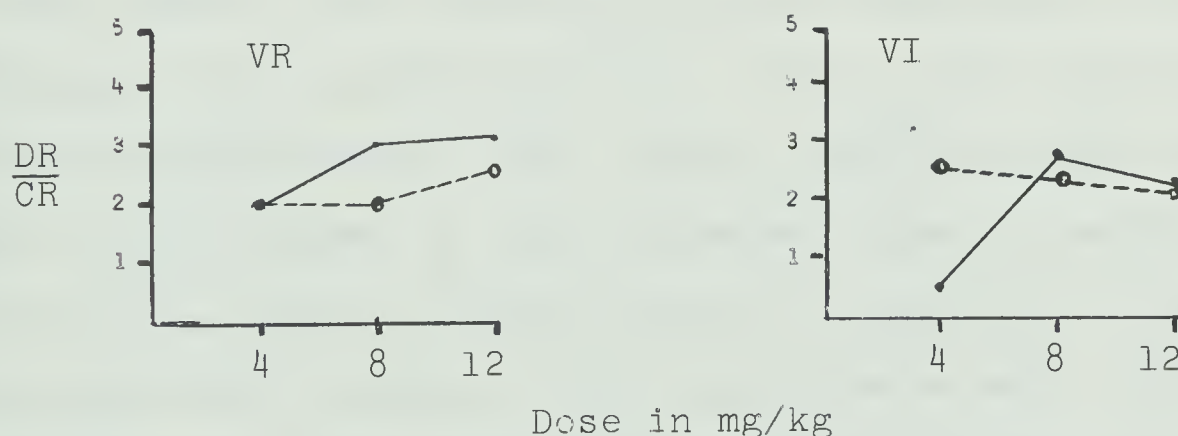


Figure 45B. Relative ratio increases in behavioral output over baseline control rates in the individual subjects. HF4 (dotted line) and HF 7 (solid line). Points represent the mean of four observations divided by their respective baseline rates.

under VR 5 conditions.

4. Under variable interval shock presentation HF4 showed small monotonic rate decreases as a function of the increase in dosage.

5. Under both VR 5 and V.I. shock presentations duration of drug effects, dependent upon the dose given, was not observed for the R*S 80 sec. animal, HF4.

6. HF7 and HF4, who both received frequent shocks under control conditions, did not, generally, show the same degree of drug-induced response rate increases as HF11 and HF8 did in the second series of drug tests.

Shock-rate/drug-rate effects

When consideration is given to control shock rates and the respective drug-induced rate changes in the individual subjects two trends were noted comparing the HF11-HF8 pair with the HF7-HF4 pair. First, those subjects receiving few shocks under control conditions (HF11 and HF8 on FR 5) show, in most instances, greater ranges in their drug-induced response rates, as compared to those subjects (HF7 and HF4 on VR 5) who receive many shocks under control conditions (See Table IV). Second, with one exception (HF7, 12 mg/kg on VR 5), a comparison of subjects in the same R*S condition but categorized as a "high" or "low" shock-rate subject showed that the "low"

shock-rate animal had a greater increase in response rate at each drug dose than the "high" shock-rate animal (i.e., HF7 vs HF11 and HF4 vs HF8; see Table V).

TABLE IV

Subject	Control Average Shocks	Response Rate Ranges							
		Control		4 mg/kg		8 mg/kg		12 mg/kg	
Series 2		FR	VI	FR	VI	FR	VI	FR	VI
HF11R*S20	7.00	8	14	50	16	30	34	39	59
HF 8R*S80	13.50	2	6	18	24	15	33	12	25
Series 3		VR	VI	VR	VI	VR	VI	VR	VI
HF7 R*S20	19.50	4	10	24	21	40	3	3	43
HF4 R*S80	27.25	2	3	6	5	11	8	15	11

TABLE V

	Subject	RPM Control	RPM*		
	Series 2		4 mg/kg	8 mg/kg	12 mg/kg
	HF 11 FR	32.12	55.45	93.46	79.90
	VI	36.16	52.16	92.69	76.69
	HF 8 FR	7.98	36.68	33.89	27.39
	VI	7.80	32.88	42.10	28.51
	Series 3				
	HF 7 VR	27.49	52.68	79.74	81.54
	VI	26.19	13.69	74.51	59.21
	HF 4 VR	4.93	9.84	10.48	11.85
	VI	5.11	12.13	11.34	10.72

*Overall RPM for four determinations.

DISCUSSION

The present study has represented a preliminary attempt to investigate the possible generalization of a proposal based upon positive reinforcement, and to more explicitly deal with the role of shock frequency as a possibly significant determinant of drug-rate interaction effects. If the original plan of the experiment could have been carried to completion without the pitfalls of schedule parameter changes, and the loss of valuable experimental subjects, a less complex and perhaps more comprehensive compilation of data would have been obtained. Rather than interpreting the results of six subjects under the same environmental conditions we have had to resort to interpretations of the effects of the drug under different environmental contingencies for each experimental subject; this has resulted in complex and often difficult interpretations of the net behavioral changes observed under the drug conditions. Generalizations and conclusions drawn on the basis of the present study are done so hesitantly and with reserve. Much more experimentation is necessary to extend explicitly, and to clarify the basic considerations that have been investigated herein.

A primary consideration that we have attempted to deal with was the proposal based upon the results of previous experimentation of Dews' (1958 a and b). Dews,

using positive reinforcement, proposed that the behavioral effects of drugs such as the amphetamines are determined largely by the pre-drug frequency of the response being studied. If the response rate is low, such drugs increase the rate (Sidman, 1956; Morse and Herrnstein, 1956; Schuster and Zimmerman, 1961; Kelleher, Fry, Deegan, and Cook, 1961; Zimmerman and Schuster 1962; Smith 1964); but when responses under control conditions occur frequently, amphetamine decreases the overall rate (Owen, 1960; Kelleher et al., 1961; Rutledge and Kelleher, 1965). This proposal acted as the basis for two of the central problems investigated in the present study: a) does methylphenidate exert similar effects as those observed with the amphetamines, and b) does Dews' drug-rate hypothesis hold for the aversive case such as free operant avoidance?

In his 1958 (b) study, Dews' in summary, had suggested that: "The number of responses made by pigeons in a fixed period of time is greatly increased by methamphetamine, when the birds are working under certain schedules (15' F.I. and F.R. 900); but it is only slightly increased when they are working under other schedules (1' V.I. and F.R. 50). It is suggested that, in appropriate doses, methamphetamine tends to reduce the number and length of the inter-response times in excess of 5 seconds but that rather larger doses also tend to prolong inter-response times shorter than one

second. Some similar effects were obtained with d-amphetamine and pipradrol." (P. 147).

The 15' F.I. and F.R. 900 schedules engendered low rates of responding while the 1' V.I. and F.R. 50 schedules engendered high rates of responding under control conditions. It should be noted that, as Dews has mentioned, overall rate increases were observed in both high and low rate subjects, but that relative to their control rates the low rate animals increased their behavioral output to a greater degree than the high rate animals under drug conditions.

In the present study high and low rates of responding (See footnote 8 p.42) were established by manipulating the response-shock interval. Those subjects remaining on the R*S 20 sec. parameter maintained high rates of responding relative to the low rates engendered by the R*S 80 sec. subjects.

Using graded doses of methylphenidate we found that, when considering overall drug-induced increases in responding, our results were consistent with those observations of Verhave (1958) and Teitelbaum and Derks (1958). The authors, in these studies, found that when training in an avoidance situation had led to a substantial tendency to respond, the effects of the amphetamines became consistent in producing an increase in rate. The overall pattern emerging from our results is that most subjects showed a

substantial tendency to an increase in response rates under all drug conditions. (See Tables I, II and III in the Result Section). Exceptions to this are HF3 in the first series of tests at 4 mg/kg (Table I) and HF7 in the third series at 4 mg/kg under VI conditions (Table III). The first and third series results under FR and VR conditions respectively, show that relative drug-induced increments in responding favor the high rate R*S 20 sec. subjects to a slight degree at the 8, 12, and 16 mg/kg dose levels. It would appear, that for these series, Dews' proposal is not applicable, (with the exception of HF4 at the 4 mg/kg level). However, the second series is quite different. Under FR conditions the low rate R*S 80 subject HF8 shows the largest degree of relative behavioral output at all three dosages administered. (See Table II and Figure 34B). This is the result we would expect to find under Dew's proposal. Even this partial verification of the proposal is uncertain, however, because unlike Dews' reinforcement schedules the presentation of the reinforcing stimuli (shocks) is not adequately controlled for under FR avoidance parameters. Control over the frequency of the reinforcing stimuli was obtained in the present study, by means of the variable interval presentation of unavoidable shock common to both subjects of the R*S 20 - R*S 80 pair. Administration of the drug upon the VI baselines resulted

in relative rate increases to a greater degree in the R*S 80 sec. subject HF8, as compared with the R*S 20 sec. subject HF11; this would offer strong support for Dews' proposal. Similar relationships are not found in the VI condition results of HF7 and HF4 under the VR/VI conditions except the 4 mg/kg dose level.

Suppression of rate of avoidance responding for HF7 under 4 mg/kg variable interval conditions is of interest (See Figures 40 and 43). Although this subject maintained a stable baseline under control conditions, it would appear at the lowest dose level given, that a facilitated discrimination may have occurred, as has been suggested by Sidman (1966):

"The effect of the free shock in keeping the animal pressing the lever even after it is no longer possible to avoid shock may be attributed to the function of the free shock in creating a spurious response-shock interval. It may also be attributed to the role of the shock as a discriminative stimulus. Until the animal learns that the shocks are actually unavoidable, the shocks continue to serve as stimuli which "tell" the animal that it is in an avoidance situation. As long as the shock continues to serve either or both

of these functions, the animal will continue to press the lever, as if avoidance were still possible. When the animal does learn that the shocks are in fact unavoidable, the shocks take on the opposite function; they then indicate to the animal that the situation is one in which avoidance is impossible. Once the shock has acquired this type of discriminative function, it may be extremely difficult, if not impossible, to recondition the animal's avoidance response" (p. 492).

The role of shock frequency as a significant determinant of drug-rate interaction effects is still not clear. The subjects in the second series of drug tests (HF11 and HF8) who had relatively few shocks under control conditions, showed in most instances, greater ranges and larger overall drug-induced rate increases than did those subjects in the third series (HF7 and HF4)¹ who took more shocks under control conditions and who displayed lesser drug-induced rate changes with smaller ranges. (See Tables IV and V). The differences found between the second and third

¹ This comparison applies only with respect to subjects of the same R*S condition: eg. HF11 vs HF7 (R*S 20) and HF8 vs HF4 (R*S 80).

series, with respect to shock frequency, are not strictly comparable. Most obvious is the fact that there were schedule differences resulting from procedure modifications. In the second series, the subjects were run under FR 5 baselines with a VI 4' presentation of common shock; the third series animals were run, however, under VR 5 baseline with a VI 2' presentation of common shocks. Inter-pair differences then cannot really be compared on the basis of shock frequency. With respect to the first series, inter-subject differences in baseline shock frequency and relative drug-induced rate changes are not reliable due to the confounding of first period drug-induced rate changes and warm-up effects. With this perspective it is apparent that the present study did not successfully clarify the role of shock frequency as a significant determinant of drug-rate interaction effects.

Some subjects (HF3 and HF9) under R*S 80 sec. parameters came to encounter serious difficulties with the FR 5 requirement. When the drug was administered prior to the experimental session, as in the first series, these subjects encountered increasing difficulties getting out of the shock-shock interval; the result was the death of one subject (HF9) and the collapse of another (HF3). In the second series two more subjects (HF7, R*S 20 sec. and HF4, R*S 80 sec.) showed increasing baseline instability.

This was accentuated in the R*S 80 sec. subject (HF4) who could not meet the FR 5 requirement within the R*S interval and who, if we had not slackened the requirement to VR 5, probably would have died, under further drug administration. Changing the parameters for these two subjects resulted in maintaining baseline performance for continuing drug tests. This change left only a single R*S 80 sec. subject (HF8) under the original conditions (FR5) of the study. We observed then that a minor scheduling change (FR5 to VR5) resulted in a major drug-behavior change in that under the VR5 condition HF4 was enabled to carry on through a complete series of drug determinations which had not been possible for most of the other similar subjects under the FR5 requirement.

In conclusion, the results of the present study may be summarized as follows:

1. Methylphenidate, on free operant avoidance behavior produces, in most instances, overall rate increases over baseline control rates. This is consistent with the results of previous experiments in which the amphetamines were employed.

2. Under variable interval 4 min. presentation of unavoidable shocks occurring in a context of FR conditions, Dews' drug-rate proposal appears to hold in that although both R*S 20 and R*S 80 sec. subjects showed moderate

absolute drug-induced rate changes, the R*S 80 sec. subject showed relative increases in behavioral output to a greater degree. The data are inconsistent for a similar conclusion for the VI behavior in the context of a VR condition.

3. Results of the present study do not warrant an explicit statement as to the role of shock frequency as a significant determinant of drug-rate interaction effects.

4. With the R*S 80 sec. subject HF4, changing a schedule parameter from FR5 to VR5 changed the behavioral topography of the animal and enabled it to complete a series of drug tests. Thus, a minor change in the scheduling arrangement may result in major drug-behavior changes.

5. Free operant ratio avoidance behavior can be maintained, over time, even in the presence of unavoidable shocks if such shocks occur in a careful program of variable interval presentation.

6. The net behavioral effects of the drug should be assessed against stable avoidance baselines. This may be achieved by administering the drug at some point in the experiment at which the beginning-of-session "warm-up" effect is no longer observed.

The following suggestions may serve as guidelines for future experimentation.

1. Further experimentation involving the manipulation of the R*S interval could be done. It appears that

if the response rate engendered by the schedule parameters is too low, that rate is not amenable to enhancement by methylphenidate. At what R*S interval then can you generate low rates (relative to R*S 20) without losing baseline avoidance control? Manipulation of the R*S interval over a range of 40, 50, 60, 70, 80, 90 and 100 seconds (holding the S*S interval constant at 5 secs.) might be done with fixed ratio avoidance.

2. Shock frequency should be held common for periods within the session against which drug effects are assessed. This can be done with careful construction of a variable interval tape to present the 'free' shock.

3. A further study might deal with the removal of shock, alternately with the VI and FR drug periods. That is, on random sessions, under drug conditions, rather than presenting aperiodic VI 'free' shock, withhold all shocks.

4. In drug studies utilizing free operant avoidance and steady state methodology the net behavioral effects of the drug should be interpreted, as in the study presented herein, in terms of both the absolute and the relative drug induced changes in behavioral output in the individual subjects.

REFERENCES

- Bernstein, B.M. and Cancro, L.P. The effect of two variables of avoidance conditioning on drug-behavior interaction. Psychopharmacologia, 1962, 3, 105-113.
- Bindra, D., and Baran, D. Effects of methylphenidyl-acetate and chlorpromazine on certain components of general activity. J. exp. Anal. Behav., 1959, 2, 343-350.
- Boren, J.J. and Sidman, M. Maintenance of avoidance behavior with intermittent shocks. Canad. J. Psychol., 1957, 11, 185-192.
- Boren, J.J., Sidman, M., and Herrnstein, R.J. Avoidance, escape, and extinction as functions of shock intensity. J. comp. physiol. Psychol., 1959, 52, 420-425.
- Brady, J.V. A review of comparative behavioral pharmacology. Ann. N.Y. Acad. Sci., 1957, 66, 719-732.
- Carlton, P.L. and Didamo, P. Augmentation of the behavioral effects of amphetamine by atropine. J. Pharmacol. exp. Therap., 1961, 132, 91-96.
- Chance, M.R.A. Aggregation as a factor influencing the toxicity of sympathomimetic amines in mice. J. Pharmacol. exp. Therap., 1946, 87, 214-219.
- Chance, M.R.A. Factors influencing the toxicity of sympathomimetic amines to solitary mice. J. Pharmacol. exp. Therap., 1947, 89, 289-296.
- Church R.M., Systematic effect of random error in the yoked control design. Psych. Bull., 1964, 62, 122-131.
- Clark, F.C. and Steele, B.J. Some observations on the interaction of chlorpromazine and free operant avoidance bursts. Psychopharmacologia, 1963, 4, 221-231.

- Cole, J., and Glees, P. Ritalin as an antagonist to reserpine in monkeys. Lancet, 1956, 1, 338.
- Cook, L., and Catania, A.C. Effects of drugs on avoidance and escape behavior. Fed. Proc., 1964, 23, 818-835.
- Cumming, W.W., and Schoenfeld, W.N. Behavior stability under extended exposure to a time-correlated reinforcement contingency. J. exp. Anal. Behav., 1960, 3, 71-82.
- Dalrymple, S.D. Effects of methylphenidate on operant behavior in rats: modification by pentobarbital and reserpine. M.Sc. dissertation, Univ. of Alberta, 1966.
- Davis, G.D. Effects of central excitant and depressant drugs on locomotor activity in the monkey. Am. J. Physiol., 1957, 188, 619-623.
- Dews, P.B. Analysis of effects of psychopharmacological agents in behavioral terms. Fed. Proc., 1958a, 17, 1024-1030.
- Dews, P.B. Studies on behavior: IV. Stimulant actions of methamphetamine. J. Pharmacol. exp. Therap., 1958b, 122, 137-147.
- Dews, P.B., and Morse, W.H. Behavioral pharmacology. Annu. Rev. Pharmacol., 1961, 1, 145-174.
- Dews, P.B. Psychopharmacology, in Experimental Foundations of Clinical Psychology. (Ed. A.J. Bachrach), Basic Books Publishing Co. 1962.
- Ferster, C.B. The use of the free operant in the analysis of behavior. Psychol. Bull., 1953, 50, 263.
- Ferster, C.B., and Skinner, B.F. Schedules of Reinforcement. New York: Appleton-Century-Crofts 1957.
- Garberg, L., and Sandberg, F. A method for quantitative estimation of the stimulant effect of an leptics on the spontaneous motility of rats. Acta Pharmacol. Toxicol., 1960, 16, 367.

- Greenblatt, E.N., and Osterberg, A.C. Correlations of activating and lethal effects of excitatory drugs in grouped and isolated mice. J. Pharmacol. Exptl. Therap., 1961, 131, 115-119.
- Gunn, J.A., and Gurd, M.R. The action of some amines related to adrenaline. Cyclohexylalkyl-amines. J. Physiol. (London), 1940, 97, 453-470.
- Hearst, E., and Whalen, R.E. Facilitating effects of d-amphetamine on discriminated-avoidance performance. J. comp. physiol. Psychol., 1963, 56, 124-128.
- Heise, G.A., and Boff, E. Continuous avoidance as a baseline for measuring behavioral effects of drugs Psychopharmacologia, 1962, 3, 264-282.
- Höhn, R. and Lasagna, L. Effects of aggregation and temperature on amphetamine toxicity in mice. Psychopharmacologia, 1960, 1, 210-220.
- Honig, W.K. (ed.) Operant Behavior: Areas of Research and Application. New York: Appleton-Century-Crofts, 1966.
- Keehn, J.D., and Chaudrey, S. Superstitious escape behavior during Sidman avoidance training. J. exp. Anal. Behav., 1964, 7, 26.
- Kelleher, R.T., Fry, W., Deegan, J., and Cook, L. Effects of meprobamate on operant behavior in rats. J. Pharmacol. exp. Therap., 1961, 131, 271-280.
- Kelleher, R.T., Riddle, W.C. and Cook, L. Persistent behavior maintained by unavoidable shocks. J. exp. Anal. Behav., 1963, 6, 507-517.
- Krueger, G.L., and McGrath, W.R. 2-Benzylpiperidines and related compounds, in Psychopharmacological Agents, Vol. I, (Ed. M. Gordon) New York: Academic Press, 1964.
- Lashley, K.S. The effect of strychnine and caffeine upon rate of learning. Psychobiol., 1917, 1, 141-170.
- Maxwell, R.A., Plummer, A.J., Povalski, H., Schneider, F., and Coombs, H. A comparison of some of the cardiovascular actions of methylphenidate and cocaine. J. Pharmacol. Exptl. Therap., 1959, 126, 250-257.

- Mechner, F., and Latranyi, M. Behavioral effects of caffeine, methamphetamine, and methylphenidate in the rat. J. exp. Anal. Behav. 1963, 6, 331-342.
- Meier, R., Gross, F., and Tripod, J. Vernindung mit nevertige synthetische zentralerregender wirkungskomponente. Klin. Wochschr., 1954, 32, 445-450.
- Mendelson, J., and Bindra, D. Combination of drive and drug effects. J. Exptl. Psychol., 1962, 63, 505-509.
- Morse, W.H. Use of operant conditioning techniques for evaluating the effects of barbiturates on behavior. In, The First Hahnemann Symposium on Psychosomatic Medicine, 1962, 275-281.
- Morse, W.H., and Herrnstein, R.J. Effects of drugs on characteristics of behavior maintained by complex schedules of intermittent positive reinforcement. Ann. N.Y. Acad. Sci., 1956, 65, 303-317.
- Owen, J.E. The influence of dl-, d-, and l-amphetamine and d-methamphetamine on a fixed ratio schedule. J. exp. Anal. Behav., 1960, 3, 293-309.
- Pavlov, I.P. Conditioned Reflexes (transl. G.V. Anrep) p. 127, New York: Oxford Univ. Press 1927.
- Rutledge, C.O. and Kelleher, R.T. Interactions between the effects of methamphetamine and pentobarbital on operant behavior in the pigeon. Psychopharmacologia, 1965, 7, 400-408.
- Schoenfeld, W.N., Cumming, W.W., and Hearst, E. On the classification of reinforcement schedules. Proc. Nat. Acad. Sci., 1956, 42, 563-570.
- Schuster, C.R., and Zimmerman, J. Timing behavior during prolonged treatment with dl-amphetamine. J. exp. Anal. Behav., 1961, 4, 327-330.
- Skinner, B.F. The behavior of organisms: an experimental analysis. New York: Appleton-Century-Crofts, 1938.
- Skinner, B.F., and Heron, W.T. Effects of caffeine and benzedrine upon conditioning and extinction. Psychol. Record. 1937, 1, 340-346.

- Sidman, M. Avoidance conditioning with brief shock and no exteroceptive warning signal. Science, 1953a, 118, 157-158.
- Sidman, M. Two temporal parameters of the maintenance of avoidance behavior by the white rat. J. comp. physiol. Psychol., 1953b, 46, 253-261.
- Sidman, M. Drug behavior interaction. Ann. N.Y. Acad. Sci., 1956, 65, 282-302.
- Sidman, M. Some notes on "bursts" in free-operant avoidance experiments. J. exp. Anal. Behav., 1958, 1, 167-172.
- Sidman, M. Tactics of Scientific Research. Evaluating experimental data in psychology. New York: Basic Books, 1960.
- Sidman, M. Reduction of shock frequency as reinforcement for avoidance behavior. J. exp. Anal. Behav., 1962, 5, 247-257.
- Sidman, M. Avoidance behavior, in Operant Behavior: Areas of Research and Application. (Ed. W.K. Honig) New York: Appleton-Century-Crofts, 1966.
- Sidman, M., Herrnstein, R.J., and Conrad, D.G. Maintenance of avoidance behavior by unavoidable shocks, J. comp. physiol. Psychol., 1957, 50, 553-557.
- Smith, C.B. Effects of d-amphetamine upon operant behavior of pigeons: enhancement by reserpine. J. Pharmacol. exp. Therap., 1964, 146, 167-174.
- Solomon, R.L., and Brush, E.S. Experimentally derived conceptions of anxiety and aversion. In, Nebraska symposium on motivation (Ed. M.R. Jones). Lincoln: Univ. of Nebraska Press, 1956, pp. 212-305.
- Stewart, C.C. Variations in daily activity produced by alcohol and by changes in barometric pressure and diet, with a description of recording methods. Am. J. Physiol., 1898, 1, 40-56.
- Stretch, R., Blackman, D., and Alexander, D. Some effects of methylphenidate on stimulus control of ratio avoidance behavior in the rat. J. exp. Anal. Behav. 1966, 9, 389-398.

- Stretch, R., and Dalrymple, S.D. Effects of methylphenidate, pentobarbital, and reserpine on behavior controlled by a schedule of interresponse time reinforcement. Psychopharmacologia, 1968, 13, 49-64.
- Stretch, R., and Skinner, N. Methylphenidate and stimulus control of avoidance behavior. J. exp. Anal. Behav., 1967, 10, 485-493.
- Teitelbaum, P. and Derks, P. The effect of amphetamine on forced drinking in the rat. J. comp. physiol. Psychol., 1958, 51, 801-810.
- Verhave, T. The effect of methamphetamine on operant level and avoidance behavior. J. exp. Anal. Behav., 1958, 1, 207-219.
- Verhave, T. Technique for differential reinforcement of rate of avoidance responding. Science, 1959, 129, 959-960.
- Verhave, T. A depressant effect of methamphetamine on avoidance behavior. Fed. Proc., 1961, 20, 395.
- Verhave, T., Owen, J.E., Jr., and Robbins, E.B. Effects of chlorpromazine and secobarbital on avoidance and escape behavior. Arch. intern. Pharmacodynamie, 1958, 116, 45-53.
- Waller, M.B., and Waller, P.F. The effects of unavoidable shocks on a multiple schedule having an avoidance component. J. exp. Anal. Behav., 1963, 6, 29-37.
- Weissman, A. Correlation between baseline nondiscriminated avoidance behavior in rats and amphetamine-induced stimulation. Psychopharmacologia, 1963, 4, 294-297.
- Zimmerman, J. and Schuster, C.R. Spaced responding in multiple DRL schedules. J. exp. Anal. Behav., 1962, 5, 497-504.

APPENDICES

Subject	RPM		Shocks	
HF8	9.29	8.43 to 10.30	10.64	6.00 to 17.57
HF4	7.91	6.62 to 9.00	12.41	6.00 to 23.50
HF3	9.87	9.18 to 11.10	17.85	13.50 to 23.50

Overall response rate per minute and average shocks per hour, for 10 consecutive sessions on R*S 80 S*S 5 FR 5, RATS HF8, HF4 and HF3. Minimum and maximum rates for responses per minute and shocks per hour are also shown.

TABLE 2

Subject	RPM		Shocks	
HF11	33.20	29.06 to 37.24	5.85	2.00 to 8.50
HF7	32.97	29.05 to 38.27	10.95	4.50 to 20.00
HF6	33.26	29.47 to 40.78	12.53	10.00 to 21.00

Overall response rate per minute and average shocks per hour for 10 consecutive sessions on R*S 20 S*S 5 FR5, RATS HF11, HF7 and HF6. Minimum and maximum rates for responses per minute and shocks per hour are also shown.

TABLE 3	40 minute periods					
	1			2		
	3			3		
SUBJECT	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	$\begin{smallmatrix} 45.32 \\ 55.81 \text{ to} \\ 75.17 \end{smallmatrix}$	$\begin{smallmatrix} 3.00 \\ 7.00 \text{ to} \\ 12.00 \end{smallmatrix}$	$\begin{smallmatrix} 32.70 \\ 40.47 \text{ to} \\ 45.38 \end{smallmatrix}$	$\begin{smallmatrix} 3.00 \\ 5.50 \text{ to} \\ 8.00 \end{smallmatrix}$	$\begin{smallmatrix} 30.30 \\ 34.21 \text{ to} \\ 36.85 \end{smallmatrix}$	$\begin{smallmatrix} 4.00 \\ 6.25 \text{ to} \\ 9.00 \end{smallmatrix}$
HF7	$\begin{smallmatrix} 42.07 \\ 57.22 \text{ to} \\ 67.85 \end{smallmatrix}$	$\begin{smallmatrix} 4.00 \\ 14.00 \text{ to} \\ 20.00 \end{smallmatrix}$	$\begin{smallmatrix} 37.97 \\ 39.32 \text{ to} \\ 40.85 \end{smallmatrix}$	$\begin{smallmatrix} 3.00 \\ 6.00 \text{ to} \\ 10.00 \end{smallmatrix}$	$\begin{smallmatrix} 31.60 \\ 33.58 \text{ to} \\ 38.00 \end{smallmatrix}$	$\begin{smallmatrix} 2.00 \\ 5.75 \text{ to} \\ 8.00 \end{smallmatrix}$
HF6	$\begin{smallmatrix} 32.72 \\ 42.83 \text{ to} \\ 56.00 \end{smallmatrix}$	$\begin{smallmatrix} 19.00 \\ 35.00 \text{ to} \\ 56.00 \end{smallmatrix}$	$\begin{smallmatrix} 33.60 \\ 37.73 \text{ to} \\ 43.47 \end{smallmatrix}$	$\begin{smallmatrix} 9.00 \\ 14.25 \text{ to} \\ 19.00 \end{smallmatrix}$	$\begin{smallmatrix} 28.62 \\ 35.89 \text{ to} \\ 45.40 \end{smallmatrix}$	$\begin{smallmatrix} 6.00 \\ 15.25 \text{ to} \\ 36.00 \end{smallmatrix}$
HF8	$\begin{smallmatrix} 12.17 \\ 22.50 \text{ to} \\ 31.37 \end{smallmatrix}$	$\begin{smallmatrix} 9.00 \\ 21.25 \text{ to} \\ 29.00 \end{smallmatrix}$	$\begin{smallmatrix} 13.45 \\ 15.11 \text{ to} \\ 17.80 \end{smallmatrix}$	$\begin{smallmatrix} 0.00 \\ 2.25 \text{ to} \\ 5.00 \end{smallmatrix}$	$\begin{smallmatrix} 10.12 \\ 12.08 \text{ to} \\ 14.20 \end{smallmatrix}$	$\begin{smallmatrix} 0.00 \\ 3.00 \text{ to} \\ 5.00 \end{smallmatrix}$
HF3	$\begin{smallmatrix} 9.37 \\ 10.08 \text{ to} \\ 11.65 \end{smallmatrix}$	$\begin{smallmatrix} 24.00 \\ 50.00 \text{ to} \\ 67.00 \end{smallmatrix}$	$\begin{smallmatrix} 11.00 \\ 16.66 \text{ to} \\ 24.17 \end{smallmatrix}$	$\begin{smallmatrix} 6.00 \\ 9.00 \text{ to} \\ 16.00 \end{smallmatrix}$	$\begin{smallmatrix} 9.35 \\ 9.39 \text{ to} \\ 11.72 \end{smallmatrix}$	$\begin{smallmatrix} 6.00 \\ 12.25 \text{ to} \\ 25.00 \end{smallmatrix}$

Overall response rates per minute and average shock per 40 minute period for four determinations of methylphenidate at 4 mg/kg dosage level. Minimum and maximum rates for responses per minute and shocks per 40 minute period are also shown.

TABLE 4	40 minute periods					
	1		2		3	
Subject	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	82.50 88.86 to 102.87	1.00 3.00 to 6.00	46.12 60.27 to 77.95	0.00 2.50 to 6.00	32.42 36.33 to 40.97	4.00 6.50 to 12.00
HF7.	68.92 77.97 to 91.10	3.00 8.25 to 12.00	55.32 58.72 to 68.27	6.00 7.00 to 9.00	35.97 41.82 to 46.12	1.00 3.50 to 7.00
HF6	77.87 100.96 to 129.85	7.00 20.50 to 37.00	37.15 46.72 to 57.12	11.00 22.50 to 32.00	31.20 33.40 to 37.65	13.00 18.25 to 28.00
HF8	12.32 17.59 to 25.35	5.00 9.50 to 16.00	13.27 25.20 to 38.25	0.00 1.75 to 6.00	10.72 14.03 to 16.35	0.00 2.75 to 4.00
HF3	7.77 27.23 to 48.40	54.00 72.50 to 95.00	15.52 26.94 to 38.65	5.00 8.00 to 14.00	9.45 11.02 to 12.57	5.00 9.75 to 19.00

Overall response rates per minute and average shocks per 40 minute period for four determinations of methylphenidate at 8 mg/kg dosage level. Minimum and maximum rates for responses per minute and shocks per 40 minute period are also shown.

TABLE 5	40 minute periods					
	1			2		
	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	75.20 86.90 to 93.10	1.00 5.50 to 11.00	61.75 72.93 to 80.47	0.00 1.25 to 3.00	46.02 54.52 to 64.12	1.00 2.25 to 5.00
HF7.	54.55 92.01 to 120.62	2.00 11.25 to 33.00	50.93 66.76 to 94.45	0.00 1.75 to 7.00	50.05 56.31 to 61.87	2.00 3.00 to 5.00
HF6	61.32 88.68 to 104.35	18.00 35.50 to 85.00	71.47 85.10 to 96.95	0.00 0 to ---	51.05 68.67 to 85.35	2.00 9.75 to 20.00
HF8	5.40 16.83 to 26.87	5.00 20.50 to 42.00	10.57 16.58 to 25.92	0.00 9.00 to 29.00	8.77 15.92 to 22.75	2.00 4.75 to 10.00
HF3 *	19.07 22.22 to 25.37	27.00 67.00 to 107.00	13.45 17.07 to 20.70	0.00 6.50 to 13.00	--- --- to ---	--- --- to ---

* Incomplete - collapsed during third interval of second determination.

Overall response rates per minute and average shocks per 40 minute period for four determinations of methylphenidate at 16 mg/kg dosage level. Minimum and maximum rates for responses per minute and shocks per 40 minute period are also shown.

TABLE 6	40 minute periods					
	1		2		3	
	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	27.52 36.94 to 46.27	6.00 15.71 to 35.00	29.40 35.50 to 41.40	4.00 6.14 to 11.00	29.07 33.54 to 39.35	3.00 5.57 to 9.00
HF7	30.62 33.74 to 35.85	29.00 36.00 to 42.00	30.65 34.43 to 27.27	6.00 16.60 to 33.00	31.95 36.27 to 42.37	3.00 8.40 to 17.00
HF6	22.25 27.08 to 32.22	49.00 61.00 to 80.00	28.67 40.75 to 54.72	9.00 16.00 to 29.00	31.27 42.03 to 53.47	7.00 11.80 to 20.00
HF8	8.67 9.42 to 11.92	4.00 13.80 to 24.00	8.07 8.74 to 16.60	1.00 6.20 to 12.00	8.32 9.92 to 12.20	0.00 7.20 to 17.00
HF3	5.57 9.73 to 13.95	28.00 38.20 to 47.00	7.50 8.49 to 10.15	10.00 21.60 to 40.00	8.07 8.57 to 9.32	12.00 23.20 to 42.00

Overall response rates per minute and average shocks per 40 minute period under saline conditions. Minimum and maximum RPM and average shocks per 40 minute period are also shown.

TABLE 7		40 minutes periods					
		2		3		4	
Subject	Condition	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	FR	29.52 32.20 to 35.12	3.00 6.00 to 8.00	30.27 32.12 to 38.25	4.00 7.00 to 12.00	29.12 32.06 to 34.92	7.00 7.66 to 9.00
					*		
	VI	29.77 33.10 to 38.17	6.00 8.62 to 16.00	29.32 36.66 to 43.05	10.00 11.25 to 12.00	28.90 34.58 to 38.82	4.00 6.50 to 15.00
HF8	FR	6.42 7.65 to 8.77	4.00 17.00 to 38.00	7.17 7.98 to 9.10	8.00 13.50 to 21.00	6.32 8.95 to 15.05	5.00 11.16 to 17.00
	VI	6.80 7.40 to 8.03	3.00 13.62 to 22.00	4.87 7.80 to 11.00	* 10.00 11.25 to 12.00	7.12 7.92 to 9.62	4.00 13.25 to 18.00

Table 7

* Both subjects receive identical frequency and temporal patterning of shocks during this period.

Overall response rates per minute and average shocks per 40 minute period under fixed ratio 5 and variable interval 4 minute control conditions. Minimum and maximum response rates per minute and average shocks per 40 minute period are also shown.

Table 8

TABLE 8		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	FR	29.00 32.30 to 36.37	12.00 14.25 to 16.00	38.82 55.45 to 89.42	1.00 3.00 to 5.00	32.62 35.03 to 36.85	1.00 3.00 to 4.00
	VI	29.20 32.69 to 36.70	6.00 10.00 to 13.00	44.60 52.16 to 60.65	* 9.00 to 11.00 to 13.00	37.26 39.93 to 46.62	1.00 2.50 to 4.00
HF8	FR	7.67 8.34 to 8.95	8.00 15.75 to 27.00	30.30 36.68 to 47.92	3.00 3.50 to 5.00	9.27 11.65 to 12.50	6.00 13.25 to 20.00
	VI	6.52 7.63 to 8.60	13.00 23.25 to 35.00	23.07 32.88 to 47.40	* 9.00 to 11.00 to 13.00	8.00 10.69 to 13.47	1.00 18.75 to 60.00

* Both subjects receive identical frequency and temporal patterning of shocks during this period.

Overall response rates per minute and average shocks per 40 minute period for four determinations of methylphenidate at the 4 mg/kg dosage level on FR 5/VI 4 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are also shown.

Table 9

TABLE 9		40		minute		periods	
		2		3		4	
Subject	RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS	SHOCKS
HF11	28.02 29.94 to 31.62	4.00 10.50 to 23.00	80.07 93.46 to 110.52	1.00 1.25 to 2.00	43.25 55.82 to 68.10		2.00 4.25 to 8.00
				*			
	31.22 32.06 to 33.77	4.00 7.75 to 12.00	75.50 92.69 to 110.17	8.00 9.75 to 13.00	33.77 39.08 to 46.62		1.00 8.50 to 23.00
HF8	6.32 7.31 to 8.45	7.00 14.75 to 23.00	26.42 33.89 to 41.60	0.00 1.25 to 4.00	9.62 13.88 to 15.87		0.00 6.00 to 16.00
				*			
	7.35 7.51 to 7.70	10.00 12.75 to 15.00	22.85 42.10 to 56.15	8.00 9.75 to 13.00	17.67 23.48 to 30.77		6.00 9.00 to 24.00

* Both subjects receive identical frequency and temporal patterning of shocks during this period.

Overall response rates per minute and average shocks per 40 minute period for four determinations of methylphenidate at the 8 mg/kg dosage level on FR 5/VI 4 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are also shown.

TABLE 10		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	FR	28.25 32.34 to 37.10	7.00 12.75 to 27.00	57.22 79.90 to 96.15	0.00 4.00 to 7.00	61.80 73.70 to 89.25	0.00 3.75 to 11.00
	VI	30.10 31.76 to 34.57	7.00 8.75 to 11.00	51.07 76.69 to 110.45	* 13.00 to 14.00	31.75 61.62 to 89.70	0.00 3.50 to 12.00
HF8	FR	6.77 7.31 to 8.30	8.00 14.50 to 30.00	22.60 27.39 to 34.97	1.00 2.75 to 4.00	20.60 29.85 to 37.60	0.00 0.25 to 1.00
	VI	6.72 7.65 to 8.02	13.00 16.50 to 20.00	18.37 28.51 to 43.30	* 13.00 to 14.00	20.46 29.18 to 41.62	0.00 3.00 to 6.00

* Both subjects receive identical frequency and temporal patterning of shocks during this period.

Overall response rates per minute and average shocks per 40 minute period for four determinations of methylphenidate at the 12 mg/kg dosage level on FR 5/VI 4 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are also shown.

Table 11

TABLE II		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF11	FR	29.85 31.41 to 32.50	4.00 6.75 to 10.00	31.12 32.41 to 34.65	4.00 6.25 to 9.00	29.52 32.45 to 35.00	7.00 8.50 to 10.00
	VI	27.32 30.99 to 33.52	6.00 13.25 to 21.00	24.65 34.52 to 39.30	* 10.00 to 12.00	29.32 31.96 to 38.07	8.00 10.50 to 20.00
HF8	FR	7.57 8.38 to 9.42	9.00 16.75 to 23.00	7.25 8.13 to 8.45	4.00 12.75 to 19.00	6.82 7.96 to 9.27	5.00 12.75 to 20.00
	VI	6.45 7.70 to 8.57	5.00 20.00 to 27.00	4.70 7.51 to 10.35	* 10.00 to 12.00	7.10 8.09 to 9.05	7.00 14.50 to 19.00

*Both subjects receive identical frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shock per 40 minute period under fixed ratio 5 and variable interval 4 minute saline conditions. Minimum and maximum response rates per minute and average shocks per 40 minute period are also shown.

Table 12

TABLE 12		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF7	VR	26.00 28.40 to 31.80	19.00 25.00 to 34.00	26.35 27.49 to 30.30	17.00 19.50 to 23.00	24.60 26.67 to 29.15	7.00 16.00 to 23.00
	VI	25.80 29.28 to 32.25	8.00 24.00 to 39.00	21.02 26.19 to 31.87	* 20.00 to 21.00	24.47 27.31 to 30.00	8.00 19.00 to 37.00
HF4	VR	4.52 4.96 to 5.45	15.00 23.00 to 32.00	4.10 4.93 to 5.45	9.00 27.25 to 44.00	4.52 5.01 to 5.70	16.00 24.50 to 36.00
	VI	4.37 5.02 to 5.85	12.00 31.75 to 55.00	3.85 5.11 to 6.30	* 20.00 to 21.00	4.82 5.49 to 6.00	12.00 25.75 to 35.00

*

Both animals receive identical shock frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shocks per 40 minute period under variable ratio 5 and variable interval 2 minute control conditions. Maximum and minimum response rates per minute and average shocks per 40 minute period are shown.

TABLE 13		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF7	VR	23.50 25.71 to 27.95	21.00 32.00 to 45.00	40.25 52.68 to 64.47	6.00 7.00 to 8.00	26.32 28.79 to 31.67	7.00 12.25 to 17.00
	VI	22.47 25.76 to 27.27	15.00 26.75 to 49.00	6.45 13.69 to 27.10	* 19.00 20.25 to 21.00	26.77 29.84 to 35.45	4.00 12.50 to 23.00
HF4	VR	4.02 4.76 to 5.15	17.00 23.00 to 41.00	7.35 9.84 to 13.02	2.00 7.25 to 14.00	6.77 7.30 to 7.77	9.00 10.75 to 12.00
	VI	5.07 5.20 to 5.37	15.00 21.00 to 32.00	9.95 12.13 to 15.00	* 19.00 20.25 to 21.00	6.05 6.82 to 7.47	7.00 10.75 to 14.00

Table 13

*

Both animals receive identical shock frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shock rate per 40 minute period for four determinations of methylphenidate at the 4 mg/kg dosage level on VR 5/VI 2 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are shown.

TABLE 14		40 minute periods					
		2		3		4	
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF7	VR	22.40 25.43 to 29.90	24.00 35.50 to 45.00	56.72 79.74 to 97.42	2.00 4.75 to 8.00	29.62 39.05 to 49.92	6.00 8.75 to 11.00
	VI	24.97 27.39 to 31.65	10.00 21.25 to 26.00	72.97 74.51 to 75.05	* 21.00 22.25 to 23.00	31.32 35.82 to 38.47	4.00 8.25 to 12.00
HF4	VR	3.97 4.48 to 5.25	17.00 31.50 to 46.00	7.10 10.48 to 17.82	3.00 6.25 to 9.00	6.15 6.58 to 7.05	5.00 8.50 to 12.00
	VI	4.50 5.06 to 5.60	14.00 21.25 to 28.00	8.07 11.34 to 15.67	* 21.00 22.25 to 23.00	5.90 6.89 to 8.17	6.00 11.00 to 21.00

Table 14

*

Both animals receive identical shock frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shock rate per 40 minute period for four determinations of methylphenidate at the 8 mg/kg dosage level on VR 5/VI 2 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are shown.

TABLE 15		40 minute periods					
Subject		2		3		4	
		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS
HF7	VR	24.80 27.51 to 31.67	13.00 26.50 to 32.00	80.25 81.54 to 82.90	1.00 6.25 to 15.00	41.52 53.69 to 66.67	0.00 1.50 to 4.00
	VI	21.07 25.76 to 30.95	12.00 26.00 to 37.00	34.00 59.21 to 77.37	* 19.00 20.25 to 22.00	36.02 42.56 to 46.47	3.00 8.50 to 17.00
HF4	VR	4.30 4.78 to 5.42	18.00 26.00 to 37.00	6.77 11.85 to 21.10	0.00 7.00 to 15.00	4.97 6.99 to 8.35	2.00 13.25 to 37.00
	VI	4.22 4.69 to 5.22	23.00 31.75 to 40.00	6.00 10.72 to 16.72	* 19.00 20.25 to 22.00	4.85 6.79 to 9.32	1.00 10.25 to 27.00

* Both animals receive identical shock frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shock rate per 40 minute period for four determinations of methylphenidate at the 12 mg/kg dosage level on VR 5/VI 2 minute baselines. Maximum and minimum response rates per minute and average shocks per 40 minute period are shown.

TABLE 16		40 minute periods							
		2		3		4			
Subject		RPM	SHOCKS	RPM	SHOCKS	RPM	SHOCKS		
HF7	VR	23.07 25.82 to 28.00	17.00 26.25 to 45.00	24.35 25.87 to 27.45	17.00 23.25 to 27.00	24.92 26.07 to 26.87	15.00 21.25 to 29.00		
	VI	23.92 25.06 to 26.50	20.00 33.75 to 42.00	17.90 21.89 to 23.42	* 18.00 19.75 to 21.00	24.62 27.02 to 28.67	25.00 32.25 to 51.00		
HF4	VR	4.12 4.72 to 5.32	19.00 29.00 to 47.00	4.50 4.88 to 5.27	16.00 23.00 to 32.00	4.42 4.83 to 5.42	21.00 23.25 to 28.00		
	VI	4.47 4.69 to 4.95	25.00 28.75 to 36.00	4.07 5.13 to 6.00	* 18.00 19.75 to 21.00	4.50 5.05 to 5.47	12.00 21.25 to 43.00		

* Both animals receive identical shock frequency and temporal patterning of shocks during this period.

Overall response rate per minute and average shock rate per 40 minute period under variable ratio 5 and variable interval 2 min. saline conditions. Maximum and minimum response rates per minute and average shocks per 40 minute period are shown.

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